

Therapeutics: Key to well being

Edited by

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Adity Sarbajna

Sandeep Poddar

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— Editorial —

Therapeutics are medications that are used to treat or prevent an illness. Drug therapy, medical gadgets, nutrition therapy, and stem-cell therapies are all examples of therapeutics. Therapeutics can be used in patients to treat the disease or its symptoms, as well as in preventative medicine and palliative care.

Tinospora cordifolia (Willd.) Miers is a well-known indigenous medicinal plant belonging to the family Menispermaceae. The herb is extensively used in traditional medicine for treatment of chronic fever related to dengue and malaria. It is also recommended as ayurvedic treatment to increase immunity and improve digestive ailments.

India, West Bengal has a sizable number of medicinal plants because of different weather conditions. West Bengal is one and only state in India where Darjeeling Himalayas are within the north and Sundarbans areas are in the south with meadowlands and uplands covering a vicinity with a variety of medicinal plants. The traditional system of public health care has been effectively used, over many years to treat illnesses in West Bengal. In tribal culture of West Bengal traditional medicine can be an awfully sound and reputed medical system. This 21st century totally believes in modern medical system, but tribal peoples avoid allopathic and homeopathic medicine to cure their disease.

Sesame plant is used for numerous purposes. It is used in different culinary processes. It also has applications in pharmaceutical, industrial, and engineering industry. Different phytonutrients, some flavonoid phenolic antioxidants, several vitamins and dietary fibre which have medicinal properties. It has other proven medicinal benefits such as anti-inflammatory, anti-microbial, anti-hypertensive, anti-pyretic, anticancer and few additional properties. As a result, the sesame plant has a bright future in the medical arena, with the potential to improve and enhance the eminence of life of mankind.

The tremendous pharmacological activities and a wealth of available literature make *Ocimum sanctum* one of the most valuable herbs in the plant kingdom. The pharmaceutical activities of the herb results from the amalgamated and synergistic interactions of the different phytochemicals present. This widespread herb is easily available in India and other neighbouring countries, growing both in wild and cultivated forms. The extensive range of the properties of its chemical constituents makes it a potential entity for more detailed clinical research. More investigations will establish the prospects of using the plant and its active novel chemical constituents in a large scale in modern medicine.

Several Covid-19 medicines are being used un-licensed due to pandemic. For this reason, a long-term data was needed for a proper evaluation in their efficiency and safety. So, this review is about a detailed investigation of several possible treatment of covid-19, which can guide pharmacist and therapist in the time of pandemic.

The cheapest and most frequently used drug in medicine is Aspirin. In the wide range of pharmacological area, it is a non-steroidal anti-inflammatory drug, including antipyretic, analgesic, and antiplatelet assets. Aspirin has been long used as a beneficial analgesic and antipyretic. Even in historical times, salicylate-containing flora inclusive of the willow had been typically used to alleviate ache and fever.

Cisplatin or cis-diamminedichloridoplatinum (II) is one of the most successful and efficient chemotherapeutic drugs for the treatment of various types of malignancies, including bladder, testis, ovary, head and neck, lung cancer, germ cell tumors, lymphomas, sarcomas, and many others. Cisplatin molecules bind with DNA to form an adduct which finally transduces several signalling pathways, resulting in apoptosis and cell death. Unfortunately, neither cytotoxicity nor apoptosis are completely generated in cancer cells. Therefore, cisplatin may have a variety of side effects that limit its use and effectiveness.

The study of distinct cultural approaches to health, sickness, and illness, as well as the nature of local therapeutic systems, is known as ethnomedicine. Ethnomedicinal research are important for the discovery of novel crude medicines from indigenous medicinal plants that have been described. Ethnobotanical research is critical for the development of new medicines derived from plant species that are part of the world's indigenous heritage. Medicinal herbs are frequently utilised as cosmetics,

flavours, oils, bitters, spices, sweeteners, pesticides, and death agents to assist relieve human misery. Monoclonal antibodies are immune system proteins that are manufactured in a laboratory. Antibodies are proteins that are produced naturally by the body that assist the immune system in recognising and destroying disease-causing organisms such as bacteria and viruses. Monoclonal antibody medicines are cancer treatments that use body's germ-fighting immune system to combat disease.

Therefore, therapeutic effect refers to the response to any therapy whose outcomes are deemed useful or favourable. This is true whether the outcome was anticipated, unanticipated, or even unintended. Consequently, therapeutics is used in patients with active disease – to treat the disease itself or its signs and symptoms – in preventive medicine, or as palliative care.

The editors would like to thank all the authors for their contribution in such varied topics that will help to create awareness about therapeutics for serving and caring for the patient in a comprehensive manner, preventing disease as well as managing specific problems. The editors are also thankful to the Principal, Surendranath College, Kolkata, India, Management of Lincoln University College, Malaysia and Lincoln Research & Publishing Limited, Australia for giving them the necessary permission to publish this book. We are also thankful to Department of Biotechnology, Government of India for providing the financial assistance. This book provides knowledge about different medicine that deals specifically with the treatment of disease and the art and science of healing. The researchers here deal with varied topics of therapeutics accordingly, to refer to the use of drugs and the method of their administration in the treatment of disease.

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FOREWORD

It is my great pleasure to introduce this book titled as "Therapeutics: Key to well being," a collection of review articles written by the undergraduate students of the four DBT STAR departments of Surendranath College, Kolkata, covering a wide range of contemporary themes on current advances in various areas of therapeutics, under able mentorship of their faculty members as mentors.

The volume consists of twelve chapters and pursues specific objectives while complementing the existing literature on different areas of therapeutic sciences. It explores the scope of future development in various related emerging fields and analyses the challenges in doing so. I extend special thanks and underline my deepest appreciation to the publisher for publishing this issue, Department of Biotechnology, Government of India for providing the financial assistance and all the editors of this book for their real hard work and sincere effort in bringing out this wonderful volume.

While I hope this collection will have particular appeal to all the new young readers in this field, I am confident that the volume will raise interest among our regular readership of scholars and practitioners elsewhere as well, thanks to the relevance and diversity of contributions compiled here in this volume.

Happy reading to all!

Dr. Indranil Kar
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Medicinal Properties of *Tinospora cordifolia* (Willd.) Miers: A Review

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ABSTRACT

Tinospora cordifolia (Willd.) Miers is a well-known indigenous medicinal plant belonging to the family Menispermaceae. The plant is commonly known as 'Giloy' or 'Guduchi' in India and is extensively found in the tropical regions of the country. The roots, stems, and leaves of this indigenous plant have been used in different herbal medicine formulations for ages, including in the treatment of jaundice, diabetes, heart disease, different types of arthritis, urinary tract infections, and as an antiseptic, to name a few. The herb is extensively used in traditional medicine for treatment of chronic fever related to dengue and malaria. It is also recommended in ayurveda to increase immunity and improve digestive ailments. In the last three decades, pre-clinical research has provided tremendous evidence of a varied range of the claimed pharmacological properties in animal models and in vitro studies, namely, hypo-glycaemic activity, anti-pyretic activity, anti-microbial activity, hepato-protective activity, neuro-protective and neuro-regenerative properties, etc. This review is aimed at an up to date compilation of the recent advancements in the field of pharmacological research in *Tinospora cordifolia*.

Keywords: *Tinospora cordifolia*, Giloy, Guduchi, Medicinal Value, Pharmacological Properties

INTRODUCTION

Tinospora cordifolia (Willd.) Miers (Family-Menispermaceae; Synonym-*Menispermum cordifolium* Willd.) is a large deciduous climbing shrub, native to the tropical areas of India, Sri Lanka, Myanmar, and other parts of South-East Asia, as well as in Africa (The Plant List, 2013). In India, it is distributed throughout the tropical regions, extending from Assam and West Bengal in the east to Maharashtra in the west, from Delhi in the north to Kerala and Karnataka in the south. *T. cordifolia* is one of the well-known traditional medicinal plants extensively used in the treatment of various diseases in Ayurveda, Unani, and Siddha medicine from ancient times. *T. cordifolia* is commonly known as 'Guduchi' in Marathi, 'Giloy'/'Gilo'/'Gilai' in Hindi, 'Gulanchar' in Bengali, 'Galo' in Gujarati, 'Gelo' and 'Amarlata' in Assamese, 'Guluchi' in Oriya, 'Gilo' in Punjabi, 'Tinospora' in English, etc. In traditional medicine, the plant extracts have been used in the treatment of dysplasia, jaundice, urinary tract infection, diabetes, heart diseases, rheumatoid arthritis, digestive diseases, and many more (Nadkarni & Nadkarni, 1976). The most important secondary metabolites of *T. cordifolia* responsible for its medicinal properties are: alkaloids like tinosporine, tinosporaside, magnoflorine, berberine, and coline; sterols like giloisterol and -sitosterol, in addition to the most common glucoside, amritoside (Choudhary *et al.*, 2013). This review is aimed at providing an up-to-date compilation status of the recent advances in research on various pharmacological properties of *T. cordifolia*.

REVIEW LITERATURE

Pharmacological properties of *Tinospora cordifolia*

In the last three decades, extensive research has provided proof of plethora of pharmacological properties of different parts of the plant (Figure 1). *T. cordifolia* is reported to have array of medicinal properties like- anti-diabetic (Stanely Mainzen Prince & Menon, 2000, 2003; Sonkamble & Kamble, 2015; Chacko, 2018; Khanal *et al.*, 2019; Vora *et al.*, 2020), anti-pyretic (Pendse *et al.*, 1977; Ashok *et al.*, 2010; Hussain *et al.*, 2015; Rakib *et al.*, 2020), hepato-protective (Bishayi *et al.*, 2002; Panchabhai

et al., 2008; Rakib *et al.*, 2020), cardio-protective (Rao *et al.*, 2005; Sharma *et al.*, 2011a; Priya *et al.*, 2017; Begum *et al.*, 2021), neuro-protective (Kosaraju *et al.*, 2014; Sharma & Kaur 2018; Birla *et al.*, 2021), anti-allergic, anti-oxidant (Sharma & Joshi, 2011; Praveen *et al.*, 2012; Prasad & Chauhan, 2019), anti-tumour (Jagetia, Nayak & Vidyasagar, 1998; Jagetia & Rao, 2006; Deepa *et al.*, 2019; Palmieri *et al.*, 2019), radio-protective (Goel *et al.*, 2004; Sharma *et al.*, 2011b; Patel *et al.*, 2013) immuno-modulatory (Bishayi *et al.*, 2002; Nageswari, Reddy & Venkatappa, 2018), anti-ulcer (Sarma *et al.*, 1995; Bairy *et al.*, 2002; Kaur, Singh & Kumar, 2014), anti-fertility (Gupta & Sharma, 2003; Ittiavirah & Rahman, 2013), anti-microbial (Jeyachandran, Xavier & Anand, 2003; Mishra *et al.*, 2014; Chowdhury, 2020), etc. Recently the plant gained attention due to reports of antiviral property against Covid-19 (Chowdhury, 2020).



Figure 1: Pharmacological properties of *Tinospora cordifolia* (Willd.) Miers

DISCUSSION

Anti-diabetic Activity:

Tinospora cordifolia has been used in the treatment of diabetes since ancient times. Various pharmacological studies have proved the hypoglycaemic properties of the plant, especially in root extracts. The anti-hyperglycaemic effect of aqueous and alcoholic extracts as well as lyophilized powder of the plant has been reported to be effective in pre-clinical trials on drug-induced diabetic animals as well as cell cultures. Oral administration of alcoholic extracts of *T. cordifolia* roots is reported to significantly reduce blood glucose and urine glucose in alloxan-dependent diabetic rats (Stanely Mainzen Prince & Menon, 2000, 2003). Aqueous solution of the plant extract significantly reduced blood glucose levels in Streptozotocin-induced diabetic rats as well (Chacko, 2018). *Tinospora* extract has been shown to have better hypoglycaemic activity when co-administered with other conventional drugs. Aqueous extract of *T. cordifolia* co-administered with drugs like metformin, sitagliptin, and glibenclamide has been reported to show better management of diabetes and its related co-morbidities in streptozotocin-induced diabetic rats compared to those administered individually (Vora *et al.*, 2020). Further, the plant extract did not show any pharmacokinetic interaction with drugs administered. The phenolic compounds present in extracts of *T. cordifolia* are suggested to be responsible for the anti-diabetic effects which act by inhibiting alpha-amylase and beta-glucosidase activity (Sonkamble & Kamble, 2015). Khanal *et al.*, (2019) identified nine secondary metabolites of *T. cordifolia* involved in modulation of proteins related to diabetes, among which, tembetarine is suggested to be the most important one responsible for anti-diabetic properties. It works by modulating the majority of diabetic proteins, specifically modulating neuro-active ligand-receptor interactions (Khanal *et al.*, 2019).

Anti-oxidant Activity:

The antioxidant property of root extracts of *T. cordifolia* has been studied for a long time. Oral administration of aqueous root extracts of the plant has shown significant antioxidant properties against alloxan drug induced diabetes rats (Stanely Mainzen Prince & Menon 1999, 2001; Stanely Mainzen Prince, Padmanabhan & Menon, 2004). Both aqueous and alcoholic extracts of *T. cordifolia* cause a decrease in the levels of marker compounds related to lipid peroxidation, namely-plasma thio-barbituric acid reactive substances and -tocopherol, and thus are suggested to reduce oxidative stress (Stanely Mainzen Prince & Menon, 1999; Stanely Mainzen Prince, Padmanabhan & Menon, 2004). It simultaneously causes an increase in the levels of glutathione and vitamin C in the test subjects, thus helping in combating free radicals (Stanely Mainzen Prince & Menon 1999). 'Giloy' extracts (5g/kg body weight) are also reported to significantly increase the reduced catalase, glutathione, and superoxide dismutase activity in drug-induced diabetic rats (Stanely Mainzen Prince & Menon, 2001; Stanely Mainzen Prince, Padmanabhan & Menon, 2004). Some reports suggest extraction methods have a prominent impact on the antioxidant properties of the plant. Praveen *et al.* (2012) observed extracts of leaves of *T. cordifolia* to score the highest antioxidant activity compared to ethyl acetate, butanol and aqueous extracts. In another report, an ethanolic extract of *T. cordifolia* leaves showed promising free radical scavenging potency that was significantly superior to aqueous and methanolic extracts of the same (Sharma & Joshi, 2011). This observation was supported recently by Prasad and Chauhan (2019), where the total phenolic content and antioxidant activity of ethanolic extracts from both stem and roots of *T. cordifolia* proved to be significantly higher than the other solvents tested. In this study, ethanolic stem extracts of the plant scored significantly better in both hydrogen peroxide scavenging (87%) and hydroxyl free radical scavenging (91%) activities (Prasad & Chauhan, 2019).

Anti-pyretic Activity:

'Giloy' is well known for its fever reducing or preventing properties in traditional medicines. Anti-pyretic activity of the plant extracts in animal models is being studied for more than three decades (Pendse *et al.*, 1977; Leghari, Muzaffar & Haq, 1984; Ikram, Khattak & Gilani, 1987; Vedavathy & Rao, 1991). Pendse *et al.*, (1977) reported the antipyretic activity of aqueous stem extract of *T. cordifolia* in albino mice, while Leghari, Muzaffar and Haq (1984) and Ikram, Khattak and Gilani (1987) observed similar activity in Himalayan rabbits. Ethanolic extracts of the *Tinospora cordifolia* stem showed very effective in reducing fever in Yeast induced pyrexia in albino rats (Vedavathy & Rao, 1991; Ashok *et al.*, 2010). Aqueous- methanolic extract of the whole plant showed anti-pyretic effect in dose dependent manner in similar animal models (Hussain *et al.*, 2015). In recent studies, methanolic extracts and its sub-fractions showed anti-pyretic activity in dose dependent manner and *in silico* studies suggested the probable mode of action for such activity to be modulated by the phytochemical, genkwanin in *Tinospora crispa* (Rakib *et al.*, 2020).

Anti-inflammatory Activity:

Aqueous extracts of *T. cordifolia* showed significant anti-inflammatory and immuno-suppressive properties in albino rats and rabbits respectively (Pendse *et al.*, 1977). Similar anti-inflammatory activity against carrageenan induced paw edema model in albino mice is reported for aqueous and aqueous methanolic extracts of *T. cordifolia* respectively (Patgiri *et al.*, 2014; Hussain *et al.*, 2015). Philip, Tom and Vasumathi (2018) elucidated the mechanism of anti-inflammatory potential of this plant at the molecular level. In this *in vitro* study, chloroform extracts of *T. cordifolia* significantly reduced up-regulation of pro-inflammatory biomarkers with minimum inhibition of cyclooxygenase-1 enzyme expression in the process, thus making the 'Giloy' an ideal plant for development of anti-inflammatory drug in future (Philip, Tom & Vasumathi, 2018).

Hypo-lipidaemic Activity:

Alternative therapy for the treatment of high blood cholesterol and other blood lipids has attracted much attention in recent days due to the increase in abnormal baseline lipid levels of adults worldwide in their

30s. Of the different herbal drugs used traditionally for such treatment aimed at side-effect-free intervention for lipid reduction in the blood, the roots of 'Giloy' are noteworthy. Different pharmacological studies supported the hypolipidemic activity of the plant in pre-clinical studies. Stanely, Mainzen, Prince, Menon, and Gunasekaran (1998) discovered a hypolipidaemic effect in *Tinospora cordifolia* root aqueous extract. In the study, aqueous extracts of the roots administered (2.5-5 g/kg body weight) to alloxan-induced diabetic rats for 6 weeks showed a significant reduction in serum and tissue cholesterol, phospholipids, and free fatty acids in test subjects. The root extract at a dose of 5 g/kg body weight showed the highest hypolipidaemic effect (Stanely Mainzen Prince, Menon & Gunasekaran, 1998). Similar activity is also reported in alcoholic extracts of the *Tinospora* roots, where oral administration of the extracts for 6 weeks resulted in a reduction of lipids in serum and tissues in the treated animal subjects (Stanely Mainzen Prince & Menon, 2003). In another study, administration of aqueous extract of *T. cordifolia* at a much lower dose, viz. 200 mg/kg body weight, decreased serum glucose, cholesterol, triglycerides, creatine kinase, and free fatty acids to a normal level when compared to that of a standard drug in diet-induced hyperlipidemic rats (Vetrivadivelan *et al.*, 2012).

Cardio-protective Activity:

Tinospora cordifolia not only reduces blood and serum lipid levels, but also provides overall protection of the cardio-vascular system, as evident from reports on cardio-protective activity in different studies conducted with alcoholic and aqueous extracts of the plant in pre-clinical studies (Rao *et al.*, 2005; Sharma *et al.*, 2011a; Priya *et al.*, 2017; Begum *et al.*, 2021). The restoration of blood supply to the ischemic tissue frequently results in injury or cellular damage, which is known medically as ischemia-reperfusion injury (IR-injury). Whole plant of *T. cordifolia* extracted with alcohol, showed a beneficial effect on partial reversion of IR-injury when pre-treated with the plant extract before inducing myocardial ischemia in rat models (Rao *et al.*, 2005). Oxidative stress is suggested to be one of the major pathways responsible for IR-injury, and thus, anti-oxidants can play an important role in preventing cellular damage progression. As discussed earlier, *T. cordifolia* is rich in anti-oxidants, which is suggested to have contributed to the cardio-protective role of the plant against IR-injury (Rao *et al.*, 2005).

In addition, Sharma *et al.* (2011a) reported similar cardio-protective activity of alcoholic extract of the whole plant of *T. cordifolia* in calcium chloride induced arrhythmia in rats. Methanolic stem extract of the medicinal plant showed a noticeable protective effect on cadmium-induced cardiotoxicity in male Wistar rats (Priya *et al.*, 2017). A recent study with aqueous leaf extracts of *T. cordifolia* by Begum *et al.*, (2021) showed similar cardio-protective potential of the plant leaf against cisplatin-induced cardiotoxicity in animal models.

Hepato-protective Activity:

The medicinal plant *Tinospora cordifolia* is used in various traditional healing systems worldwide including preventing damage to the liver due to various reasons. *T. cordifolia* extract protected the liver in carbon tetrachloride induced hepatic damage in rats. Administration of the plant extract (100mg/Kg body weight) significantly reduced biomarkers for liver damage like- reduction in levels of serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP) and bilirubin in blood of test subjects. *T. cordifolia* extract also eliminated the immune-suppressive effects of carbon tetrachloride, suggesting *Tinospora* sp. to be a promising herb for development of protection against liver damage (Bishayi *et al.*, 2002). Rakib *et al.*, (2020) recently reported similar hepato-protective property by *in silico* approach in carbon tetrachloride induced animal model with crude organic extract and various sub-fractions of *Tinospora crispa*. 'Giloy' have also been reported to have protective property against anti-tubercular drug induced hepatic damage when administered alone or in combination with *Phyllanthus emblica* (Panchabhai *et al.*, 2008).

Neuro-protective Activity:

Loss of dopaminergic neurons, the main source of dopamine in the mammalian central nervous

system, is associated with Parkinson's disease, which is categorised as one of the most well-known neurological disorders in human beings. The majority of conventional drugs used in treatment have numerous unfavourable side effects. The ethno-medicinal plant, 'Giloy', has neuro-protective properties as revealed by various studies involving Parkinson's disease in animal models. Ethanolic extracts of *Tinospora cordifolia* showed significant protective function against 6-hydroxy dopamine induced Parkinson's disease in rat models by reducing accumulation of iron and protecting dopaminergic neurons (Kosaraju *et al.*, 2014). The neuro-protective and neuro-regenerative capacity of the plant was also reported against glutamate-induced excitotoxicity in the *in vitro* study conducted by Sharma and Kaur (2018). In the study, comparative analysis of different extraction processes was also evaluated, suggesting butanol extract to be the most potent in neuro-protective activity in comparison to hexane, chloroform, and ethyl acetate extracts following fractionation of the aqueous extract of *Tinospora cordifolia* (Sharma & Kaur, 2018). Birla *et al.*, (2021) studied molecular mechanisms of the neuro-protective activity of the plant extract in a Rotenone intoxicated mouse model through a proteomics approach. The study demonstrated the therapeutic effect of the plant extract via regulation of multiple pathways, leading to the protection of dopaminergic neurons.

Anti-microbial Activity:

The antimicrobial activity of the indigenous medicinal plant 'Giloy' has been reported against a number of bacteria, both Gram positive and Gram negative, against fungi as well as against viruses, thus supporting the traditional use of the plant as an antiseptic agent. The plant's ethanolic extract has been shown to have significant antibacterial activity against Gram positive bacteria such as *Staphylococcus aureus* and Gram negative bacteria such as *Escherichia coli*, *Proteus vulgaris*, *Enterobacter faecalis*, *Serratia marcescens*, and *Salmonella typhi* (Jeyachandran, Xavier, and Anand, 2003). Mishra *et al.* (2014) reported that hydro-methanolic extract of *Tinospora cordifolia* exhibits anti-microbial activity against *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*, while ethanolic extracts of the plant show significant antibacterial property against *E. coli* as well. Methanolic extract of the root and stem of *T. cordifolia* exhibited anti-microbial activity against bacteria (*viz. E. coli* and *B. subtilis*) as well as fungi (*viz. Aspergillus niger* and *Candida sp.*), indicating a wide range of antimicrobial activity (Prasad & Chauhan, 2019). Berberine, a phytochemical constituent of *T. cordifolia*, has been found to have the potential for regulation of a key protein function, thus controlling viral replication in Covid-19 disease progression in *in silico* studies (Chowdhury, 2020). This finding further extends the use of 'Giloy' as natural medicine for its antimicrobial properties.

Anti-cancerous Activity:

Decades of research on *Tinospora sp.* suggests that the plant has anti-cancer potential. Extracts of *T. cordifolia* are reported to exhibit significant anti-proliferative properties in pre-clinical trials with animal models (Jagetia, Nayak & Vidyasagar, 1998; Jagetia & Rao, 2006; Deepa *et al.*, 2019; Palmieri *et al.*, 2019). Jagetia, Nayak, & Vidyasagar (1998) reported the ability of "Giloy" extracts to effectively kill HeLa cells *in vitro* in a dose-dependent manner. Interestingly, the plant extract was equal to or more efficient than the common chemotherapeutic drug, doxorubicin. The ability of *T. cordifolia* to kill HeLa cells, which is comparable to cancerous cell lines in many ways, opened the avenue for future studies on anti-proliferative properties of the plant.

Ehrlich Ascites Carcinoma (EAC) is a spontaneous breast cancer in mice and one of the most common models for pre-clinical studies on anti-tumour drugs and cancer progression. Test subjects transplanted with EAC showed dose dependent response to *T. cordifolia* extracts (dichloromethane extract) for tumour-free survival with optimal activity at 50mg/kg body weight in mice (Jagetia & Rao, 2006). Intervention with an optimal dose of 'Giloy' extract increased the life span of the mice from 19 days (control group) to 90 days (test subjects) in survivors (100%). The mode of action for tumour free survival is suggested to be due to the cytotoxic effect of the plant extracts on the tumour cells via a decrease in glutathione concentration and an increase in lipid peroxidation (Jagetia & Rao, 2006).

Deepa *et al.* (2019) suggested in a recent systematic review of *T. cordifolia* as a potent anti-cancerous

plant based on more than 300 published works that berbarine and its analogue palmatine alkaloids are some of the most important phytochemicals present in the plant responsible for its anti-cancerous properties. According to a study on human colon cancer cell lines, the purified alkaloid berberine from *T. cordifolia* works on cancer cells by specifically targeting more than 30 genes involved in cancer cell proliferation and differentiation (Palmieri *et al.*, 2019). Berberine is also known to have a cytotoxic effect on cancer cells by promoting apoptosis without any side effects.

Radio-protective Activity:

Pre-clinical trials show a promising future for the medicinal plant *Tinospora cordifolia* in preventing radiation injury. Gamma irradiation in male mice models results in decrease in body weight and 100% mortality. Administration of stem extracts of *T. cordifolia* before irradiation with gamma rays showed impressive protection as evident from different parameters, including, nearly 76% survival rate, prevention of weight loss, increase in spleen colony forming unit, etc. Administration of the plant extract even restored total lymphocyte count after 2 weeks of exposure in the test subjects (Goel *et al.*, 2004). Sharma *et al.*, (2011b) also reported similar radio-protective function of *T. cordifolia* extracts, administered orally 30 minutes before gamma radiation in male mice. The test subjects showed 100% survival rate with significant increase in body weight, tissue weight and other related parameters compared to control sets (receiving gamma radiation without administration of 'Giloy' extract before exposure). Furthermore, the experimental animals pre-treated with the plant extract showed amelioration of increased lipid peroxidase and decreased glutathione concentration due to irradiation in testes (Sharma *et al.*, 2011b). Radio-protective and cyto-protective activities of the plant extract containing cordifolioside A are also noted in mice when administered through peritoneum 15 days prior to gamma ray irradiation (Patel *et al.*, 2013).

Anti-ulcerous Activity:

The pharmacological affectivity of *Tinospora cordifolia* against ulcer is reported since many years supporting its use in Ayurveda for treatment of ulcer. Sarma *et al.* (1995) reported anti-ulcer property of the ethanolic extracts of *T. cordifolia* roots against stress induced ulcer. The protective activity of the plant extract was even comparable with the anti-ulcer drug diazepam. Similar anti-ulcer activity was observed with alcoholic extracts from whole plant of *T. cordifolia* in different drug induced ulcer models in addition to stress-induced ulcers (Bairy *et al.*, 2002). Moreover, in this study, the ulcer-protective efficiency of the plant extract was comparable to common anti-ulcer drugs famotidine and misoprostol in drug induced ulcer models. Pyrolic ligation induced ulcer is another common model for study of anti-ulcer drugs, where accumulation of gastric acid leads to ulcer formation in the stomach. *T. cordifolia* extracts showed impressive anti-ulcer property against Pyrolic ligation induced ulcer and ethanol induced ulcer rat models with reduced ulcer index, gastric volume and gastric acidity (Kaur, Singh & Kumar, 2014).

Anti-fertility Activity:

Traditional and ethno-medicine recommends the plant 'Giloy' for its anti-fertility properties, however, there are limited number of reports supporting the traditional claim. Of the few reports available, Gupta and Sharma (2003) observed oral administration of *T. cordifolia* stem extracts caused significant reduction in testicular weight, weight of seminal vesicle and ventral prostate, more than 70% decrease in spermatids and reduction in serum testosterone levels in male rats. Similar results were observed in male Albino Wistar rats fed with aqueous extracts of the plant (100mg/kg body weight) for 2 months suggesting spermicidal and anti-androgenic activity of *T. cordifolia* stem (Ittiavirah & Rahman, 2013). These preliminary studies suggested contraceptive effect of the plant 'Giloy', however, more studies regarding mode of action, dosage and active principals taking part in the activity must be investigated in future, to assure safe usage of the plant.

Anti-stress Activity:

In the Ayurvedic system, "Giloy" is often recommended for its rejuvenating and adaptogenic properties.

Stress causes havoc in the human physiological system in addition to prominent deterioration of mental health. Herbal safe anti-stress adaptogens help in combating depression, improving cognitive power and memory. Research shows anti-oxidants combat oxidative stress, a major outcome of mental stress discussed above, *Tinospora cordifolia* is rich in anti-oxidant properties. Sarma *et al.* (1996) reported the anti-stress activity of ethanolic extracts of the plant administered at 100mg per kg of body weight in a pre-clinical trial, and the results were comparable with those of the common anti-depressant drug diazepam. The probable mode of action for the plant to act against depression is suggested to work by either increasing the levels of amines, namely, norepinephrine, serotonin and dopamine or inhibiting degradation of the same (Mutalik & Mutalik, 2011). Preliminary clinical trials also showed significant improvement in patients with mental stress in combination with yoga, even comparable to diazepam (Biswas, Saha & Maity, 2015). However, the limited number of studies in this field calls for further research on the dosage of the herb, mechanism of action, as well as interactions with other drugs, to be recognised in modern medicine.

Immuno-modulatory Activity:

Aqueous and ethanolic extracts of *T. cordifolia* stem are reported to modulate the immune-suppressive activity of cyclophosphamide, a common medicine used in chemotherapy and to suppress immunity (Manjrekar, Jolly & Narayanan, 2000). The alcoholic extracts also inhibited drug-induced anemia, however, the aqueous extract was suggested to be more potent in immune-modulation compared to the ethanolic extract of the plant (Manjrekar, Jolly & Narayanan, 2000). Similar results were observed in rats treated with calcium chloride, where administration of *T. cordifolia* extracts inhibited the immuno-suppressive effect of calcium chloride (Bishayi *et al.*, 2002). Stem and leaf extracts of the plant also ameliorated the immuno-suppressive effects of azidothymidine (a common drug used in treatment of AIDS) in pre-clinical trials (Nageswari, Reddy & Venkatappa, 2018).

The immuno-modulatory function of *T. cordifolia* is suggested to be due to the synergistic action of multiple bioactive compounds, of which cordifolioside A and syringin are already known to have immuno-modulatory properties (Sharma *et al.*, 2012). Additionally, 5 more immuno-modulatory active compounds have been identified for the plant, showing a significant increase in phagocytosis and nitric oxide concentration, as well as increased production of ROS (Sharma *et al.*, 2012).

CONCLUSION

Tinospora cordifolia ('Giloy'), an indigenous medicinal plant of India, is well known in traditional herbal medicine for its plethora of medicinal properties. The plant is very commonly found in the dry deciduous forests of tropical India and is employed in the treatment of fevers, diabetes, heart diseases, and in the prevention of kidney and liver damage, to name a few. This review focused on the recent advances in research elucidating the pharmacological properties of the plant *T. cordifolia*. The traditional use of the 'Giloy' plant in the treatment of diabetes is well supported by the different studies performed, mainly due to the presence of various compounds inhibiting the α -amylase and β -glucosidase enzymes. Tembetarine, an important secondary metabolite responsible for the plant's anti-diabetic properties, and is thought to work by modulating diabetes-related proteins. An important traditional use of 'Giloy' to treat high fever is well supported by the pre-clinical studies in *T. cordifolia* as well as *in silico* studies in *T. crispa*. The plants score well in anti-oxidant properties and thus also have impressive anti-inflammatory and anti-cancerous activities, as evident from the observations in animal models.

Multiple studies have shown its hepato-protective, cardio-protective, immuno-modulatory, neuro-protective, and anti-microbial properties, validating its use in the treatment of jaundice, heart diseases, and against neuro-degenerative diseases like Parkinson's disease. The plant scores well in anti-microbial activity against a wide range of microbes, including bacteria, fungi, and viruses. A recent study on the anti-viral properties of active phytochemicals present in *Tinospora cordifolia* against viral replication of Covid-19 opened a new avenue for research and development of a much needed herbal drug against the pandemic causing virus. A few reports are available supporting the anti-fertility

activities of the plant, which need to be elucidated further for the safe administration of "Giloy" in the treatment of various diseases.

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Some Traditional Medicinal Plants of West Bengal: A Short Review

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ABSTRACT

In India, West Bengal has a sizable number of medicinal plants which is because of different weather conditions. West Bengal is that the one and only state in India where Darjeeling Himalayas are within the north and Sundarbans areas at the south with meadowlands and uplands covering a vicinity with a variety of medicinal plants. A medicinal plant is any plant in which one or more than one of its body parts hold materials that are used for remedial motives. Medicinal stuffs are extracted from many different parts of a plant like leaves, seeds, fruits, flowers, barks, roots and many more. More than half of the medicinal plants have been used in rehabilitating bloating, constipation, diarrhea, nausea, vomiting, dermal problems like swelling, burning, itching and irritants etc. As medicinal plants get improved empirical and commercial attentiveness, there is an increasing demand on the uncultivated plant inhabitants from which almost all traditional medicinal plants are yielded. But there are some considerable important zones at cultivation of medicinal plants in West Bengal like impoverished equipment, scarcity of profitable materials, economic situation and bewildering cultivation etc. for better yielding. Besides that, ongoing increase in human population is one among the starting points for rethinking about cultivation and medicinal administration of our state, as our economy system and sustenance of societies primarily depend on forests' gifts. In future, this review work will enrich the ethnomedicine branch of Botany and provide new information about various uses of medicinal plants.

Keywords: *Tribal Communities; Ethnomedicine; Medicinal Plants; West Bengal*

INTRODUCTION

We all know that the entire mankind has been directly dependent on the flora since the distant past. In addition to food, clothing and shelter uses of innumerable medicinal plants by man are specially mentioned in most ancient scriptures of all civilizations. In the prehistoric age of India, Maharshi Charaka was considered as father of Ayurveda as a large number of medicinal plants and their uses is mentioned in his famous book, "Charaka Sanhita". About 70% of Indian population inhabits in rural areas and many of them reside in the vicinity of forest (Datta *et al.*, 2014). They also use various plant parts as food, medicines and in many other purposes for their daily livelihood (Kala *et al.*, 2006). Use of plants as a source of medication has been a onetime and important practice of the health care system in India since ancient times (Mondal *et al.*, 2015). Several studies on them have been executed in some parts of India, over the last few decades. The tribal groups use those medicines which are mostly collected from plant sources. Through this review, the different types of medicinal plants and their uses in various districts of West Bengal have been highlighted. This state has a vast number of medicinal plants especially in tribal areas due to its changeable climatic conditions. West Bengal possesses about 850 species of medicinal plants. In the year of 2007, MoEF (Ministry of Environment & Forests, now as Ministry of Environment, Forest and Climate Change) and FRLHT (Foundation for Revitalization of Local Health Traditions) together with State Forest Department of West Bengal conducted a CAMP (Conservation Assessment and Management Prioritization) workshop and they released a list of forty six medicinal plant species for further plant-conservation (Mukherjee, 2018). More than half of the population of various developed countries have unanimously agreed on the accessibility, non-somnolent and anesthetized use of medicinal plants. But there are some major discussed areas at cultivation of medicinal plants in West Bengal like impoverished infrastructure,

deficiency of higher-ranking materials, economic circumstances and bewildering cultivation etc. A large number of medicinal plants used in Murshidabad, Nadia, Hooghly, Burdwan and North Bengal have been reviewed. Hence, there is a need to document all the uses of various medicinal plants for further research works and disease treatment (Mistry, 2015).

LITERATURE REVIEW

Traditional Medicinal Plants of West Bengal

Traditional medicine is one in every of the popular terms of cognitive content in our society. The indigenous or traditional knowledge comprises of an unlimited assemblage of information regarding the uses of plants material for health motives. All the plants which are specially mentioned in the Table 1 are used as medicine in various parts of West Bengal. These are used predominantly by regional people and also the plant or plant parts are easily available in the local markets or village markets. This review work indicates the requirements of preservation of medicinal plants and explores the long run prospect of research on this matter.

Table 1: List of some Traditional Medicinal Plants in West Bengal

Sl. No.	Local Name	Scientific Name	Family	Plant Parts	Medicinal Uses
1.	Grit Kumari	<i>Aloe vera</i>	Xanthorrhoeaceae	Leaves,pulp	Burns, wounds, inflammations.
2.	Neem	<i>Azadirachta indica</i>	Meliaceae	Leaves, bark	Prevent malaria, skin infection etc.
3.	Tulsi	<i>Ocimum sanctum</i>	Lamiaceae	Leaves	Treat common cold, asthma, fever.
4.	Amrul	<i>Oxalis corniculata</i>	Oxalidaceae	Whole plant	Used for spinal-muscular stiffness.
5.	Gulancha	<i>Tinospora cordifolia</i>	Menispermaceae	Stem	Stem boiled-water control blood sugar.
6.	Basak	<i>Justicia adhatoda</i>	Acanthaceae	Leaves	Leaf boiled water prevent cough.
7.	Thankuni	<i>Centella asiatica</i>	Apiaceae	Leaves	Prevent chronic dysentery and blood stool.
8.	Helencha	<i>Enydra fluctuans</i>	Asteraceae	Leaves	Purify blood and prevent weakness.
9.	Kalmegh	<i>Andrographis paniculata</i>	Acanthaceae	Leaves	Leaves' paste soup prevent worm, fever, cough, chronic diseases.
10.	Karola	<i>Momordica charantia</i>	Cucurbitaceae	Leaves, fruit	Leaves and fruit juice prevent diabetes, allergy etc.
11.	Kulekhara	<i>Hygrophila auriculata</i>	Acanthaceae	Leaves	Leaves' juice increases hemoglobin and it is used in treatment of anemia.
12.	Lajjabati	<i>Mimosa pudica</i>	Mimosaceae	Root	Used to prevent leucorrhea.
13.	Chirota	<i>Swertia chiratia</i>	Gentianaceae	Whole plant	Prevent liver problems.
14.	Ashok	<i>Saraca asoca</i>	Detarioideae	Bark	Used in menstrual problems.
15.	Futki	<i>Melastoma malabathricum</i>	Melastomataceae	Leaves	Prevent burnt issues.
16.	Nagmoni	<i>Dracaena bulbifera</i>	Asparagaceae	Leaves	Leaves' paste prevents insect bite wounds.
17.	Bel	<i>Aegle marmelos</i>	Rutaceae	Fruit, seed	Fruit and seed prevent stomach problems.
18.	Gadhal Pata	<i>Paederia scandens</i>	Rubiaceae	Leaves	Leaves' paste prevent leucorrhea and extract used to treat night blindness.
19.	Dhatura	<i>Datura stramonium</i>	Solanaceae	Seed	Seed used to treat dog bite wound.

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20.	Halud	<i>Cucurma longa</i>	Zingiberaceae	Rhizome	Used to prevent skin inflammations.
21.	Nishinda	<i>Vitex negundo</i>	Verbenaceae	Leaves	Leaves used to increase brain memory.
22.	Ada	<i>Zingiber officinale</i>	Zingiberaceae	Rhizome	Used in digestion treatment and wound pain relief.
23.	Dandakalash	<i>Leucas plukenetii</i>	Labiataeae	Seed, Leaves	Seed paste gives relief from insect bites.
24.	Mithapata	<i>Scoparia dulcis</i>	Scrophulariaceae	Leaves	Leaves' paste used to control pneumonia.
25.	Tentul	<i>Tamarindus indica</i>	Fabaceae	Stem bark	Bark ass used to prevent wounds.
26.	Shatamuli	<i>Asparagus racemosus</i>	Liliaceae	Root, leaves	Hyper-acidity, peptic ulcer, aphrodisiac
27.	Nayantara	<i>Catharanthus roseus</i>	Apocynaceae	Roots, leaves	Prevent diabetes.
28.	Curry pata	<i>Murraya koenigii</i>	Rutaceae	Bark, root, leaves	Prevent stomachic problems.
29.	Shiuli	<i>Nyctanthes arbor-tristis</i>	Oleaceae	Leaves	Prevent inflammation.
30.	Kesutthe	<i>Eclipta alba</i>	Asteraceae	Whole plant	Used in hepatitis treatment, an antidote in scorpion sting.
31.	Bherenda	<i>Ricinus communis</i>	Euphorbiaceae	Leaves	Used in treatment of arthritis.
32.	Haritaki	<i>Terminalia chebula</i>	Combretaceae	Fruit, bark	Used in dental care and chronic heart diseases.
33.	Sajna	<i>Moringa oleifera</i>	Moringaceae	Root, bark, leaves, seed	Used as abortifacient.
34.	Methi	<i>Trigonella foenum graecum</i>	Papilionaceae	Leaves, seed	Used in antidiabetic, hypotensive treatments.
35.	Bakul	<i>Mimusops elengi</i>	Sapotaceae	Unripe fruit	Used to treat loose teeth.
36.	Swetchandan	<i>Santalum album</i>	Santalaceae	Wood	Cure acne problems.
37.	Dhudhi	<i>Euphorbia hirta</i>	Euphorbiaceae	Leaves	Prevent urea-related problems.
38.	Kanchan	<i>Bauhinia variegata</i>	Caesalpiniaceae	Roots, leaves	Prevent diarrhea, piles, worms
39.	Bahera	<i>Terminalia bellirica</i>	Combretaceae	Fruit, bark	Prevent bile-stimulant, anemia, and bronchitis.
40.	Kolke	<i>Tabernaemontana divaricata</i>	Apocynaceae	Latex, flower	Prevent diabetes, inflammation.
41.	Jaba	<i>Hibiscus rosa sinensis</i>	Malvaceae	Roots, leaves, Flower,	Prevent fever, skin diseases, and inflammations.
42.	Ashwagandha	<i>Withania somnifera</i>	Solanaceae	Root, leaves	Extract used in sound sleep, joint pains, inflammation, sexual impotency.
43.	Kakmachi	<i>Solanum nigrum</i>	Solanaceae	Whole plant	Prevent swellings, flatulence, and dyspepsia.
44.	Sati	<i>Curcuma zedoaria</i>	Zingiberaceae	Rhizomes	Used as tonic, particularly prescribed to ladies after childbirth.
45.	Dhoney	<i>Coriandrum sativum</i>	Apiaceae	Fruit	Fruits used as digestive component and ant vomiting agent.
46.	Genda	<i>Tagetes erecta</i>	Asteraceae	Leaves	Leaves' juice applied on cuts, wounds to stop bleeding.
47.	Puin sak	<i>Basella alba</i>	Basellaceae	Root	Root used to treat tuberculosis.
48.	Swarnalata	<i>Cuscuta reflexa</i>	Cuscutaceae	Whole plant	Whole plant juice used to treat jaundice.

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49.	Lankajoba	<i>Malvaviscus arboreus</i>	Malvaceae	Flower	Flower is used to treat stomach problem.
50.	Barokuchichak phang (Rava)	<i>Angiopteris evecta</i>	Marattiaceae	Rhizome	Rhizome sap with talmishri consumed to cure leucorrhoea.
51.	Segoon	<i>Tectona grandis</i>	Verbenaceae	Leaves	Leaf juice used to treat irregular menstrual cycle.
52.	Harjora	<i>Cissus quadrangularis</i>	Vitaceae	Stem	Stem extract is used to treat broken bone.
53.	Astapata	<i>Houttuynia cordata</i>	Saururaceae	Whole plant	Whole plant used in stomach problems.
54.	Dulaltulsi	<i>Ocimum basilicum</i>	Labiatae	Leaves	Freshleaves' juice used as drops to treat earache.
55.	Jongli dopati	<i>Impatiens trilobata</i>	Balsaminaceae	Root	Root used to treat migraine pain.
56.	Lalchita	<i>Gomphrena globosa</i>	Amaranthaceae	Leaves	Leaves are used to stop bleeding.
57.	Anaras	<i>Ananas comosus</i>	Bromeliaceae	Leaves	Leaf extract to kill worms.
58.	Piyara	<i>Psidium guajava</i>	Myrtaceae	Bark	Bark used to treat child dysentery
59.	Golmorich	<i>Piper nigrum</i>	Piperaceae	Seed	Seeds are used to treat cough and cold.
60.	Hatisur	<i>Heliotropium indicum</i>	Boraginaceae	Root	Root extract is used in eye treatment.
61.	Manasa	<i>Euphorbia nerifolia</i>	Euphorbiceae	Leaves and stem	Leaves' paste used as kajal for eye infection.
62.	Sarpagandha	<i>Rauvolfia serpentina</i>	Apocynaceae	Root and leaf	Used to prevent blood pressure and hypertension.
63.	Jastimadhu	<i>Scoparia dulcis</i>	Scrophulariaceae	Leaves	Prevent cough and cold.
64.	Assam lata	<i>Chromolaena odorata</i>	Asteraceae	Leaves	Used to treat cut wounds.
65.	Rosun	<i>Allium sativum</i>	Amaryllidaceae	Bulb	Used to treat body pain and cough.
66.	Bhuikamri	<i>Merremia emarginata</i>	Convolvulaceae	Leaf	Used for Chronic blood dysentery.
67.	Harjora	<i>Cissus quadrangularis</i>	Vitaceae	Whole plant	Cured fracture wound and treat constipation.
68.	Babla	<i>Acacia nilotica</i>	Mimosaceae	Latex, leaf	Used for treat weakness and indigestion, acidity.
69.	Man-kachu	<i>Alocasia macrorrhiza</i>	Araceae	Stem	Used to prevent piles.
70.	Arhar	<i>Cajanus cajan</i>	Papilionaceae	Leaf	Leaf juice prevent jaundice.
71.	Tala Kachu	<i>Coccinia grandis</i>	Cucurbitaceae	Leaf	Leaf oil prevent migraine pain.
72.	Karpoor	<i>Cinnamomum camphora</i>	Lauraceae	Oil	Prevent insect bite.
73.	Peyaj	<i>Allium cepa</i>	Liliaceae	Bulb	Used to treat conjunctivitis, insect bite.
74.	Vasaka	<i>Adhatoda vasica</i>	Acanthaceae	Leaves, flowers, fruits	Used to treat coughs.

(Source: Bose et al., 2015; Choudhury et al., 2013; Das and Ghosh 2017; Datta et al., 2014; Dey et al., 2010; Ghosh 2008; Mistry 2015; Mukherjee, 2018)

DISCUSSION

The traditional system of public health care has been effectively used for over many years to treat illnesses in West Bengal. In tribal culture of West Bengal traditional medicine can be an awfully confidential and reputed medical system. This 21st century totally believes in modern medical system but tribal peoples avoid allopathic and homeopathic medicine to cure their disease. Their dearth of up-to-date education and intense faith in natural efficiency are indirectly in command of this. Most of the standard knowledge of medicinal plants seems to be restricted to the elder people of any tribal area

(Datta *et al.*, 2014). Besides that, in every tribal culture there is a special community called 'Vaidya', who are erudite about various medicinal plants and their uses. Details of the implementation of the plants for countless objectives are passed along by way of verbal communication only and these have been hypercritically exploited from them. (Choudhury *et al.*, 2013). Most of the ethnobotanical studies confirmed that the leaves are the main portion of the plant utilized in the treatment of diseases (Mandal *et al.*, 2020). But the various segments of plants can carry dissimilar vigorous elements in the plant. Hence, any part of the plant can be harmful when on the other hand, use of another portion of that same plant can be safe. The medicinal properties of these plant species have made an impressive contribution within the origin and evolution of the many traditional herbal therapies. These lore systems have begun to disappear with the passage of our time because of scarcity of written documents and comparatively low income in these traditions (Tripathi *et al.*, 2013). Over past some years, the medicinal plants have retrieved an intensive acceptance in herbal medicine due to its minor after effect, compared to the allopathic medicines. The traditional medicinal practitioners prepare paste, powder, pills and solutions from one plant or mixture of plants for the villagers and hence, they are considered as doctor within the tribal areas (Mondal *et al.*, 2015). Excess of plants have been used in rehabilitating bloating and excess gas, constipation, diarrhea, nausea and vomiting, abdominal pain, dermal problems like, swelling, burning, itching and irritants etc. But sometimes it has been observed that because of lack of well studies about the right methods of using medicinal plants, variety of individuals may die by countless side effects. So, during preparation of these medicines the traditional medicinal practitioners stay in their mind and take some proper precautions mind like amount of plants' parts used, dosage and solvent etc. The colossal assortments of these species from native environment are destroying vegetation too (Das & Ghosh, 2017) and also according to the practitioners or vaidyas, the new young generations are minimal engross to pick up and make use of the traditional treatment for alleviating various types of health problems (Tripathi *et al.*, 2013). Besides that, there are some pitfalls in cultivation and marketing of medicinal plants in province like absurd harvesting, less knowledge, infertile and unsuitable lands and many more. Therefore, developing the pre- and post-cultivation procedures including standard plant materials, irrigation, fertilizer, plant protection, employing fresh techniques to reinforce the assembly system, enlarging the effective plant-tissue culture system for profitable quality plant materials, inspiring the young generations such schemes are expected to help within the assembly of appreciable number of medicinal plants in West Bengal. The use of traditional medicinal plants would surely impact a notable mark on ethnomedicine branch of Botany similarly as in the commercial fields of West Bengal in future (Sarkar & Kalyani, 2005).

CONCLUSION

Villages and tribal areas of West Bengal are an important source and also the secret treasure of traditional medicinal plants. Almost in every corner of the West Bengal plants are always used as medicine. Traditional practitioners are the foremost source of knowledge on medicinal plants and about their uses. This ethno medicinal learning are transferred from one generation to different generation. Medicinal use and knowledge about these plants are marked as many small racial groups. Era, social construct, proficiency of the locals was found to be remarkable points when the quality knowledge of herbal medicines was bothered. But due to this rejuvenation and loss of biodiversity in now every day, it has noticed a significant decrease within the ethnic knowledge, moreover within the traditional medicinal branch of Botany. Preservation of these traditional medicinal should lean utmost importance during this region to forestall the rapid loss of ethno botanical wealth. Apart from the seventy four traditional medicinal plants mentioned in the review there are also other ethno medicinal plants which are very useful and important for curing various ailments and future research works. Necessary steps should be taken to forestall the extinction of these highly medicinally important plants. For reducing the ecological diversity eradication a few expedients should be grasped like record of rare medicinal plants, proper coaching services to farmers and also the villagers who are engaged in cultivation of medicinal plants, establishment of herbal gardens in house land areas, inspiring the young generation about the medicinal plants etc. So, the probability of procreation and

cultivation of the plant should be examined to grasp the aim of defendable development. Further research on these plants may end in the innovation of unique researches and studies and also it should come up with a brand-new perspective of supportable enlargement.

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An Overview of the Properties and Pharmaceutical uses of Bioactive Compounds from Sesame (*Sesamum indicum L.*)

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ABSTRACT

Sesame (*Sesamum indicum L.*, family Pedaliaceae) is undeniably a significant cash crop in the oil-seed sector. It has multiple bioactive compounds such as phytosterols, tocopherol, homologues, lignans etc. which are good for health. Lignans are formed because of the oxidative coupling of -hydroxyphenylpropane. Sesamin, sesamol, sesamolin, and sesaminol are the most important lignans in terms of medicinal and pharmacological properties. These lignans have been extensively researched and are considered to have multiple benefits. These benefits are its antioxidant, anti-aging, anti-inflammatory, anti-diabetes and anti-cancer properties. These lignans have the potency to target modern chronic diseases, which can progress to clinical diseases. The most common type of long-lasting disease is rheumatic inflammatory disease. It disturbs the sustenance structures and different parts of the body and can progress to cancer. Tocopherols are a critical part of the human diet. Different tocopherol homologues are found in sesame seeds. These include α -tocopherols, γ -tocopherols, and δ -tocopherols. This crop is also a significant source of bioactive peptides, phytates, phytosterols and polyunsaturated fatty acids although the usability of these compounds are unclear. This chapter discusses the functional significance and medicinal utility of various bioactive constituents existing in sesame seeds.

Keywords: *Sesame; Bioactive Components; Lignans; Sesamin; Phytosterols*

INTRODUCTION

Sesame is a very important annual cash crop in the world. This oilseed crop is one of the world's oldest cultivated plants. From the ancient times sesame seeds are raised in tropical regions. Seeds of *Sesamum indicum* is used as a traditional health food in East Asia, and its oil is used in natural Indian and Chinese naturopathy medicine to boost energy and avoid ageing (Kumar & Singh, 2015). The Pedaliaceae family contains approximately 16 genera and 60 species, with *Sesamum* being the most important genus group.

Quoting morphological and cytogenetic affinities between domesticated sesame and the wild south Indian *S. mulayanum* Nair., accompanied by several archaeological proofs of its cultivation in of the Indus Valley's Harappa area between 2250 and 1750 B.C. Bedigian (2003) validated that sesame was first domesticated in India. It is known as tiland raashi in Oriya and is known as tiland raashi in Gujarati and Bengali. It is known as tiland raashi in Hindi/Urdu. The term sesame derives from the early Egyptian sements, Arabic simsim and Coptic semsem (Home Cooking, 1998).

Three main commercial products obtained from sesame are its seeds, seed-oil and meal. Sesame seeds are represented as a symbol of immortality in Hindu legends. Sesame seeds were one of the earliest crops to be used for edible oil production (Carvalho *et al.*, 2001). Sesame is used as a component in various foods. When roasted, sesame seed has a nutty flavour. Bread, breadsticks, cookies, chocolate, and ice cream are all delicious when made with roasted natural sesame seed. Cakes with seeds are popular in Greece. Mechanically hulled sesame seed is used to make bakery and candies, as well as the creamy, sweet and wholesome tahini. Tahini is high in protein and an

excellent source of energy. Sesame flour is a tasty, creamy, light brown powder made from sesame seeds. Sesame flour is high in protein especially rich in amino acids methionine and tryptophan. Sesame seeds have three times the calcium content of a comparable amount of milk (Home Cooking, 1998). India produces a wide variety of sesame varieties with varying grades, each unique to the region. Sesame seeds are harvested twice a year and are available all year. India was a dominant and one of the world's oldest sesame producers.

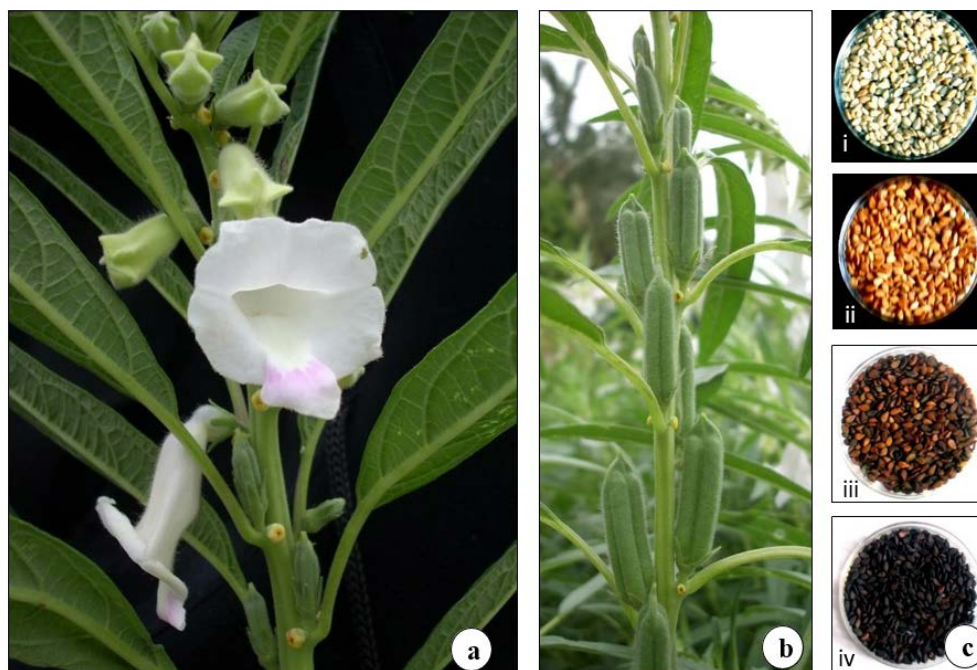


Figure 1: a) *Sesamum indicum* twig with flowers b) Fruits of Sesame c) Seeds of Different Sesame Accessions – i. Swetha Til ii. Uma iii. Madhvi iv. TMV-4

LITERATURE REVIEW

Sesame seeds have a 50-60% oil content and almost 85% poly unsaturated fatty acids (Latif & Anwar, 2011). It has a strong resistance to oxidative rancidity and can be stored for an extended period of time (Abou-Gharbia, Shehata & Shahidi, 2000; Yen & Shyu, 1989). The active constituents of sesame oil have a variety of pharmacological properties, including decreasing blood lipids (Hirata *et al.*, 1996) and arachidonic acid levels (Shimizu *et al.*, 1991), reducing blood cholesterol levels (Hirata *et al.*, 1996; Chen *et al.*, 2005; Visavadiya & Narasimhacharya, 2008), anti-inflammatory function (Utsunomiya *et al.*, 2000; Hsu *et al.*, 2005), anti-proliferative activity (Yokota *et al.*, 2007), increasing the amount of hepatic fatty acid oxidation enzymes (Ashakumary *et al.*, 1999), lower hypertension (Nakano *et al.*, 2007) and shows neuroprotective effects against hypoxia or brain damage (Cheng *et al.*, 2006). So far, sesame has been found to be the most efficient food for increasing the access of tocopherol among biological resources (Cooney *et al.*, 2001; Jiang *et al.*, 2001; Lemcke-Norojarvi *et al.*, 2001). Sesame's utility as antiseptics and bactericides has increased because of these qualities.

Sesame is also high in lignans, which are a class of bioactive phenolic compounds that include sesamin, episesamin, sesamol, sesamol, and -tocopherol (Jeng & Hou, 2005). They are, however, most abundant in sesame seed and sesamin is the most abundant isomer (1520 6.8 mol/100 g) (Liu, Saarinen & Thompson, 2006, Liang *et al.*, 2015). Raw sesame oil contains 0.5–1.1 percent sesamin and 0.2–0.6 percent sesamol, which ensures to the oil's medicinal properties because these lignans are said to have high antioxidant properties (Kumar & Singh, 2015). These lignans are responsible for sesame oil's superior oxidative stability and long shelf life. The majority of modern sesame research

has centred on particularly the two major oil-soluble lignans, sesamin and sesamol (Budowski & Markley, 1951; Fukuda & Nakata, 1999). Sesamin has been linked to a number of biochemical actions, which helps in the production of pro-inflammatory prostaglandins, provides protection against ethanol and carbon tetrachloride-induced liver damage, increases the absorption of -tocopherol, and has anti-carcinogenic properties in animals. Although, the exact mechanism of some of these effects is unknown, it has been suggested that sesamin plays a proactive role and that sesamin's metabolites are responsible for the physiological consequences (Penalvo *et al.*, 2005). Sesamin undergoes oxidative demethylenation of methylene dioxyphenyls in rat liver, resulting in catechol or methoxycatechol, which are significant antioxidant moieties as mentioned by Nakai and colleagues (2003). Sesamin also protects us against breast cancer type diseases (Penalvo *et al.*, 2005; Liu, Saarinen & Thompson, 2006). In rats, sesamin has been found to decrease blood pressure, lower serum lipids, and prevent cholesterol absorption and production. (Kumar & Singh, 2015). Cephalin, a sesame seed phospholipid, has been shown to have hemostatic activity. Sesame oil has a wide range of medicinal and pharmacological uses. It has mild laxative, soothing, and demulcent properties. As a poultice, the seeds and fresh leaves can be used. Seeds have been shown to have antibacterial activity against *Staphylococcus*, *Streptococcus* and common skin fungi such as athlete's foot fungus. According to Sirato-Yasumoto *et al.*, 2001, the oil possesses high density lipoprotein cholesterol (HDL) and lower low-density lipoprotein cholesterol (LDL). Lignans are abundant in refined sesame oil. In addition to antioxidants, sesame oil includes a high quantity of linoleate in triglyceride form, which inhibits the proliferation of malignant melanoma cells preferentially (Smith & Salerno, 1992). As a viable alternative to diesel fuel, the focus has recently switched to the manufacturing of biodiesel from sesame seed oil. Ethnobotanical and therapeutic benefits of this commercially important, nutritionally dense oilseed should be studied for its improved utilisation.

DISCUSSION

Pharmacological activity of sesame:

Anti-inflammatory and anti-pyretic activity

The anti-inflammatory activity was determined by inhibiting paw edoema caused by carrageenan (an edematogenic substance) injection into the rat's right hind paw's sub-plantar area. Their findings confirmed anti-inflammatory action of sesamin and oil of sesame by preventing pleural exudate production and leucocyte migration (Patel, Muruganathan & Gowda, 2012; Wu *et al.*, 2019).

The antipyretic activity of the oil is equivalent to that of paracetamol. In one research, sesame oil taken as a dietary supplement was found to have analgesic, antipyretic, and anti-inflammatory properties in animal models (Saleem *et al.*, 2011).

Anti-microbial activity

Sesame contains inherent antibacterial effects against a wide range of skin infections, including infection by *Streptococcus*, *Staphylococcus* and common skin fungi like athlete's foot. *Streptococcus* and other common cold germs are killed by it when gargled down the throat. It is beneficial to people who have psoriasis or dry skin. It functions as a natural UV protector. Sesame oil has the highest antimicrobial activity and is comparable to standard Kanamycin. It also has the highest zone of inhibition against *Salmonella typhi*. It was discovered that sesame oil has antibacterial activity against *Streptococcus mutans*, *Lactobacilli acidophilus* and total bacteria (Anand *et al.*, 2008).

Effects of sesamin on hypertension

Several in vitro and in vivo studies demonstrate sesamin's antihypertensive effects. According to Li and colleagues' research, giving in monocrotaline-induced hypertensive rats, sesamin (50 mg and 100 mg) for four weeks decreases proper ventricular systolic blood pressure and mean pulmonary arterial pressure. (Li *et al.*, 2015). Sesamin's antihypertensive properties have also been observed in humans. Use of 60 mg sesamin containing for four weeks among middle-aged men and women who were mildly

hypertensive showed reduction in both Systolic and diastolic blood pressure at the end of the trial on twelve subjects (Miyawaki *et al.*, 2009). Epidemiological studies recommend that lowering blood pressure by 2–3 mmHg can slow the progression of CVDs. As a result, little drop in systolic and diastolic blood pressure caused by sesamin may be sufficient enough to lower the risk of developing cardiovascular disease (Miyawaki *et al.*, 2009). Sesamin's antihypertensive properties are also being studied in patients suffering from rheumatoid arthritis, who are at a higher risk of developing CVDs (Helli *et al.*, 2016). Sesamin has also been investigated as a possible inhibitor of the arachidonic acid metabolite 20-hydroxyeicosatetraenoic acid (20HETE) (AA). The renin-angiotensin system (RAS) has been found to interact with 20-HETE and affect blood pressure control, potentially contributing to hypertension aetiology. (Hoopes *et al.*, 2015).

Sesame in lipid metabolism

Due to its chemical composition, dietary consumption of sesame oil has a high potential for condition improvement by preventing postprandial lipemia or lipid oxidation. Even though several studies on the effect of sesamin on lipid metabolism are available, just a few studies that have used whole sesame oil as a diet are available (Chavali, Zhong & Forse, 1998). It appears to have lipid peroxidation as well as the lipid profile. It is clear that sesame, which is high in lignans, has a greater impact on serum triacylglycerol levels and hepatic fatty acid oxidation. As a result, eating lignan-rich sesame causes physiological functions that alters lipid metabolism in a possibly advantageous way. Sesamol has been demonstrated to help in oxidative stress management caused by lipopolysaccharides and to activate the phosphatidylinositol 3-kinase/Akt/endothelial nitric oxide synthase pathways (Ying *et al.*, 2011) Sesame seed coat contains a lot of ethyl protocatechuate. It has antioxidant properties. In humans, it inhibits LDL oxidation. It is also used to keep foods with a high fat content fresh (Asghar, Majeed & Akhtar, 2014).

Wound healing properties

At the injury site, free radicals are produced, which are identified to impede healing by damaging cell membranes, nucleotides, proteins and lipids. Quite a few antioxidants, such as curcumin and vitamin E, have been described to protect tissues from oxidation damage in this context. Antioxidants have been proven to aid in wound healing. Sesame oil has antioxidative action potential, which assists in the prevention of oxidation regarding harms and stimulate the remedial procedure (Fukuda *et al.*, 1986; Pascoe *et al.*, 1987). In experimentally induced rats, both seeds and oil of *S. indicum* enhance wound healing. Topically applied gel comprising sesame seeds or oil, or oral ingestion of seeds or oil, significantly increase breaking strength, wound contraction, and epithelialization period in incision, excision and burn wound models (Kiran & Asad, 2008).

Sesame in Atherosclerosis

Sesame oil may effectively obstruct the creation of atherosclerosis lesion due to the harmonious interactions of fatty acid and non-saponifiable compositions (Bhaskaran *et al.*, 2006). An altered type of sesamol (INV-403) is used to improve its characteristics and is being studied for its influence on atherosclerosis. INV-403 is a new modified lignan derivative that slows the development of atherosclerosis by modulating IKK2 and nuclear factor-B signalling. (Ying *et al.*, 2011).

Anti-cancer properties

In vitro studies have revealed that sesame oil prevents the development of malignant melanoma cells and human colon cancer cell proliferation (Smith & Salerno, 1992). Consuming sesame seeds raises plasma -tocopherol and boosts vitamin E activity, both of which have been linked to a reduced danger of cancer and heart disease. Sesame seed cephalin has blood clotting activity. Sesame fiber has traditionally been used as an anti-diabetic, anti-tumor, anti-ulcer, cancer preventive, cardio-protective and laxative. Sesame seed contains myristic acid, which has cancer-preventive effects (Chakraborty, Sharma & Kaushik, 2008). Anticancer properties of sesame are summarized in Table -1.

Table 1: Anticancer Properties of Sesame Lignans

Sesame lignans	Types of Cancer controlled by sesame lignans	Reference
Sesamin	Chronic Myeloid Leukemia	Harikumar <i>et al.</i> , 2010
	Myeloma	Harikumar <i>et al.</i> , 2010
	Breast Cancer	Yokota <i>et al.</i> , 2007; Truan, Chen & Thompson, 2012; Lee <i>et al.</i> , 2011; Harikumar <i>et al.</i> , 2010; Akl <i>et al.</i> , 2013
	Cervical Cancer	Dou <i>et al.</i> , 2018
	Colon Carcinoma	Harikumar <i>et al.</i> , 2010
	Human Hepatocellular Carcinoma	Deng <i>et al.</i> , 2013
	Human Lung Adenocarcinoma	Harikumar <i>et al.</i> , 2010
	Pancreatic Cancer	Harikumar <i>et al.</i> , 2010
	Prostate Cancer	Jeng & Hou, 2005; Harikumar <i>et al.</i> , 2010
	Malignant Melanoma	Srisayam, Weerapreeyakul & Kanokmedhakul, 2017
Sesaminol	Lymphoid Leukemia	Namiki, 2007; Miyahara <i>et al.</i> , 2001
	Breast Cancer	Watanabe <i>et al.</i> , 2017
	Colon Carcinoma	Watanabe <i>et al.</i> , 2017
	Lung Adenocarcinoma	Watanabe <i>et al.</i> , 2017
	Melanoma	Watanabe <i>et al.</i> , 2017
Sesamol	Acute Myeloid Leukemia	Geetha <i>et al.</i> , 2015
	Chronic Myeloid Leukemia	Fujimoto <i>et al.</i> , 2010
	Lymphoid Leukemia	Miyahara <i>et al.</i> , 2000
	Breast Cancer	Jacklin <i>et al.</i> , 2003
	Colon Adenocarcinoma	Shimizu <i>et al.</i> , 2014
	Colon Carcinoma	Khamphio, Barusrux & Weerapreeyakul, 2016
	Human Hepatocellular Carcinoma	Liu <i>et al.</i> , 2013; Liu <i>et al.</i> , 2017
	Lung Adenocarcinoma	Siriwarin & Weerapreeyakul, 2016; Siriwarin <i>et al.</i> , 2018
	Human Malignant Melanoma	Srisayam, Weerapreeyakul & Kanokmedhakul, 2017
	Mouse Melanoma	Kumar <i>et al.</i> , 2011
	Two-Stage Mouse Skin Carcinogenesis	Kapadia <i>et al.</i> , 2002
	Mouse Leydig tumor	Chen <i>et al.</i> , 2011
Sesamolin	Burkitt's lymphoma	Kim & Lee, 2015
	Prostate Cancer	Jeng & Hou, 2005
	Human Malignant Melanoma	Srisayam, Weerapreeyakul & Kanokmedhakul, 2017

Other Medicinal Uses

Sesame oil is used to treat a variety of long-term illnesses like hepatitis, diabetes, and migraine as it has been established by the recent studies conducted by Ayurvedic physicians in Holland. These effects are supported by major migraine pathophysiological theories including the neural and sensitization theories. Tumor-suppressing properties are present in sesame flower extract (Bhaskaran *et al.*, 2006). Sesame oil contains nutritious, demulcent, and moisturizing qualities and is utilized as an intramuscular solvent. It's also been known to be used as a laxative. The leaves contain a gummy substance that, when combined with water, produces a rich, tasteless mucilage that is used to treat infant-cholera, diarrhoea, dysentery, menstrual irregularities, poly-urea, stomach problems, cataract, boils, carbuncles, major burns, skin diseases, alopecia, and as a tonic (Morton, 1990). The unsaponified portion of plant-derived oil contains phytosterols. Phytosterols account for 66% of total sterols in sesame oil. They function as an anti-cholesteric substance. Because their structure is similar to oestrogen, they can be used in oral contraception (Asghar, Majeed & Akhtar, 2014).

Future research aspects

It is preferable to choose sesame cultivars which are having high contents of sesamol and sesamin as they have high benefits on human health. There are wide use of sesame seeds and products in India. However, it is still not fully known what the profiles of sesamin and sesamol of these cultivars are. Hence, studies should be conducted on Indian sesame cultivars to determine their sesamin and sesamol contents. Till date, there is no vivid information about the mineral distributions of sesame seeds. After the seed testa is removed, sesame seeds are usually considered for food uses. Hence, analysis of the dehulled sesame seed is also required. It is also unknown where minerals are found in embryonic tissue. Estimates of diversity in cultivated plants validate the conservation approaches and aid in the selection of initial material for breeding programs. Diversified crop measures have typically been limited to assessing genome polymorphism at the DNA level. Selected morphological characteristics have been detected sporadically, and therefore the content of important chemical components has been identified, but chemical phenotypes have not been extensively and methodically incorporated in diversity surveys. Therefore, to explain the association between metabolic and genome diversity, non-targeted metabolic profiling of sesame can be used.

CONCLUSION

Sesame plant is used for numerous purposes. It is used in different culinary processes. It also has applications in pharmaceutical, industrial, and engineering industry. Different phytonutrients, some flavonoid phenolic antioxidants, several vitamins and dietary fiber which have medicinal properties come from sesame. It has other proven medicinal benefits such as anti-inflammatory, anti-microbial, anti-hypertensive, anti-pyretic, anticancer and few additional properties. As a result, the sesame plant has a bright future in the medical arena, with the potential to improve and enhance the eminence of life of mankind.

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A Synoptic Review on the Pharmacological Properties of *Ocimum sanctum* L.

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ABSTRACT

Ocimum sanctum L. (Synonym *Ocimum tenuiflorum* L.) belongs to the family Lamiaceae and is hailed to be very unique amongst the most sacred plants in India. It is a medicinally important plant as mentioned in traditional systems of treatment. This plant has been reported to possess antidiabetic, antifungal, antimicrobial, antioxidant, antifertility, anticancer, hepatoprotective, antispasmodic, and anti-inflammatory properties. This therapeutic potential of the plant is attributed mainly to the active ingredient, Eugenol, a phenolic compound along with other phytochemicals. Here, we attempt to present a synoptic compilation of the scientific reports of the pharmacological properties and significant pharmaceutical uses of the plant.

Keywords: *Ocimum Sanctum* L.; Eugenol; Pharmacological Properties

INTRODUCTION

Ocimum sanctum L. (Synonym *Ocimum tenuiflorum* L.) belongs to the family Lamiaceae, is the most prominent species of its genera (The Plant List, 2015). It is native to the Indian sub-continent and is cultivated in many countries of Southeast Asia. It is known worldwide for its medicinal, religious, ceremonial and ethnobotanical significance. This perennial herb ranging within a height of 30-60 cm has a distinctive aroma of its own. It has an upright, pubescent stem with branches. The herb has simple, petiolate leaves which are ovate in shape with slightly serrated margins and a subacute apex, arranged in a decussate phyllotaxy (Fig.1). Flowers are arranged in terminal spikes, with flowers having bilabiate corolla. It is popularly known as Holy Basil or Tulsi. Darrah (1974) identified two cultivars that are commonly found, namely - Rama Tulsi and Krishna Tulsi bearing green leaves and purple leaves respectively.



Figure1: *Ocimum Sanctum* Plant

The whole plant with all its parts – leaves, stem, root, flower and seeds – have been used for curing a variety of ailments, by the practitioners following the traditional systems of medicine. According to the Ayurvedic Pharmacopeia of India (Government of India, 1999), the powdered form of the leaves of this plant has been used in different dosages for the treatment of a variety of illnesses including the respiratory disorders, cough and cold, skin and taste disorders, and for treating problems related to worms in the gastrointestinal parts of the body (Singh & Chaudhuri 2018). In order to establish the therapeutic values in modern medicine, several researches have been conducted to study the pharmacological effects of the various extracts of the plant and use them purposefully targeting specific ailments.

LITERATURE REVIEW AND DISCUSSION

Nutritional Value:

O. sanctum contains many phytonutrients including vitamins A and C, and minerals like calcium, zinc and iron. Pattanayak *et al.*, (2010) investigated and reported about the contents of protein, carbohydrate, fats, phosphorous, calcium and iron. Among these, the protein content was found to be the highest at 4.2 gm followed by carbohydrate at 2.3 gm and fat 0.5 gm of fat per 100gm.

Chemical composition:

The leaves of *O. sanctum* consist of volatile oil (0.7%) and shows the presence of various compounds like phenolics, flavonoids, neolignans, triterpenoids and derivatives of fatty acid. Eugenol, ursolic acid, carvacrol, linalool, caryophyllene, are some of the major components in the volatile oil extracted from the leaves. The flavanoids like orientin and vicenin and flavones like apigenin, isothymusin are isolated from the aerial parts of the plant. There is more than approximately 20% of fixed oil (18–22%) along with carbohydrates in the form of polysaccharides, unsaponifiable β -sitosterol and mucilage in the seeds. Seeds of this plant are one of the chief sources of fixed oils such as oleic acid, stearic acid, palmitic acid and linolenic acid (Bano *et al.*, 2017). However, the chemical constituency of the *O. sanctum* with the essential oils could depend on an array of factors like the origin, climatic conditions and also the nature of the cultivar from which the extract have been sourced (Beatović *et al.*, 2013).

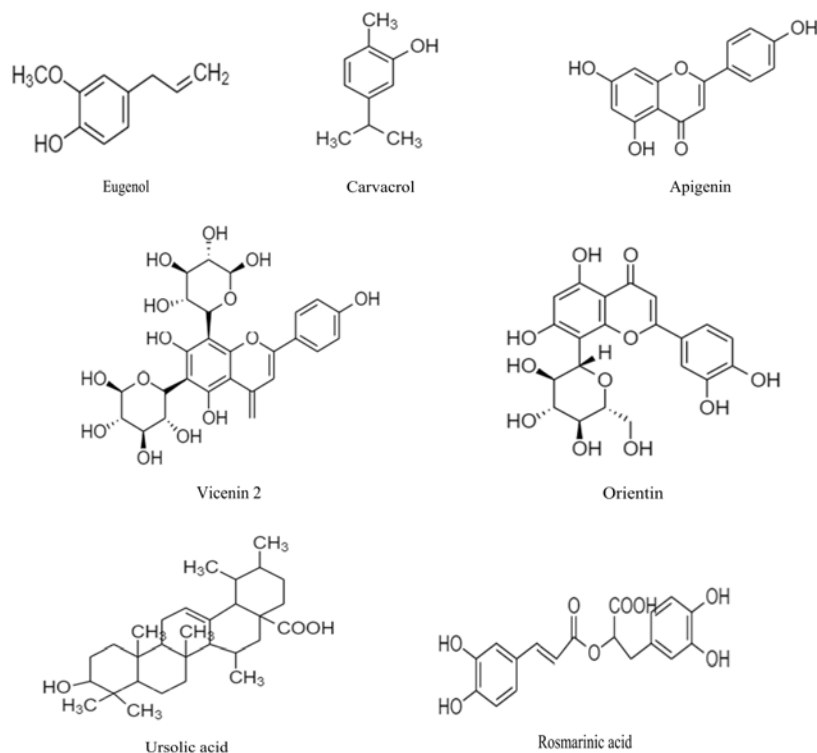


Figure 2: Chemical Structures of Some of the Important Phytochemicals Present

Pharmacological properties of *O. sanctum*:

Antimicrobial activity:

Alcoholic solvent extracts of *O. sanctum* showed wide spectrum inhibition against *Escherichia coli*, *Shigella*, *Enterobacteria* and species of *Staphylococcus* like *S. aureus* (Rahman *et al.*, 2011). It has also been proved to act against *Pseudomonas aeruginosa*, *Salmonella typhi*, *Klebsiella pneumoniae*, *Proteus*, *Candida albicans*, *Mycobacterium tuberculosis* and *Micrococcus pyogenes* (Mishra & Mishra, 2011).

The flavanoids, orientin and vicenin, obtained from leaves of *O. sanctum* showed positive results against some bacteria that cause urinary tract infection in humans (Ali a & Dixit, 2012).

The essential oil, obtained from the flower spikes and leaves of *O. sanctum*, at concentrations of 4.5% and 2.25% could have bacteriostatic effect on *Staphylococcus aureus*, methicillin resistant *S. aureus* (MRSA) and *Escherichia coli*, by inhibiting their growth (Yamani *et al.*, 2016).

Antioxidant & Anti-inflammatory activity:

Anti-inflammatory or cyclooxygenase inhibitory activity have been established using purified extracts of aerial parts of the plant, by the virtue of phytochemicals like eugenol, rosmarinic acid, apigenin, isothymusin, cirsilineol, etc (Kelm *et al.*, 2000). Antioxidant potentiality of essential oils of the plant parts was observed by Salles Trevisan *et al.*, (2006) and Gupta *et al.*, (2006).

Antidiabetic activity:

Gholap and Kar (2004) suggested that the concentrations of the carbohydrate – glucose and cortisol could be decreased in the serum, as studied in male mice, by the usage of *O. sanctum* functioning to exhibit a hypoglycaemic and antiperoxidative effect.

Reports have been given by Hannan *et al.*, (2006), that the chemical compounds present in the leaf extracts of *O. sanctum* affect the insulin secretory pathways and stimulate its production exhibiting insulinotropic effects, as examined with ethanolic extracts and five partition fractions on perfused rat pancreas, isolated rat islets and clonal rat BRIN-BD 11 cell line. Thus, from the study, the antihyperglycaemic potential of *O. sanctum* could be established.

Fractions of ethyl acetate derived from the alcoholic leaf extract of *O. sanctum* made with ethanol was reported to significantly reduce the level of fasting blood sugar, along with serum total cholesterol and triglyceride in diabetic rats induced with alloxan (AIDR). Petroleum ether and chloroform fractions too along with the fraction of extract made from the ethyl acetate were found to play a role in the elevation of liver glycogen levels, which otherwise are reduced in severely diabetic rats, thereby exhibiting an antidiabetic property with hepatoprotective effects (Khan *et al.*, 2010).

The extract of the plants roots made with methanol, have been reported to exhibit antidiabetic potential on fasting blood glucose levels in rats which were induced to be diabetic with streptozotocin; in these rats the blood glucose levels were reduced to normal using the extract. Three new active constituents were characterized along with ursolic acid and palmityl glucoside (Ahmad *et al.*, 2012).

O. sanctum have been reported to be a useful source of novel antidiabetic compounds and as a dietary supplement for managing the complications arising due to type-2 diabetes (Hannan *et al.*, 2015).

Antigenotoxic activity:

The leaf extract exerts a protective effect against genetic damage induced with Cr Hg-I (Babu & Maheswari, 2006). Siddique *et al.*, (2007) reported the action of *O. sanctum* extract against any genotoxic damage in the in vitro mammalian cells subjected to cyproterone acetate.

Radioprotective activity:

Uma Devi *et al.*, (2000) isolated the two flavonoids, orientin and vicenin, from the leaves of *O. sanctum* that are water-soluble and both the flavonoids were tested for their effect on the peroxidation of lipids caused by radiation and their antioxidant activity in adult mice. From the study, it was reported that the flavonoids provided significant protection against radiation lethality and chromosomal aberration, by inhibiting free radical formation.

Anticarcinogenic activity:

The extract of the leaves of *O. sanctum* made with ethanol have been found to regulate enzymes such as cytochrome P-450, cytochrome-b5 and aryl hydrocarbon hydroxylase, that metabolize carcinogens in the mice liver and elevate their activities, along with increasing the reduced glutathione levels (Banerjee

et al., 1996).

The seed oil of this plant could delay tumor incidence and thereby enhance longer survival when administered on Swiss albino mice. The antioxidant property of the plant can be attributed to this chemopreventive potential (Prakash & Gupta, 2000).

There are reports of both the aqueous and ethanolic extracts of *O. sanctum* being effective in reducing the volume of the tumour in Sarcoma-180 affected mice followed by an increase in their lifespan. It has also been found to have effects on human fibrosarcoma cells in the in vitro condition, clearly indicative of its anticancer activity (Karthikeyan *et al.*, 2008).

The flavanoid, vicenin-2, present in *O. sanctum* was found to be very efficient as a novel compound to restrict the proliferation of prostate cancer when used in combination with docetaxel when administered in mice (Nagaprashantha *et al.*, 2011).

In a similar study, Baliga *et al.*, (2013) reported that the two flavanoids, vicenin and orientin were effective in protecting normal cells from the tumoricidal damage caused by gamma-radiation.

Antifertility activity:

The leaves of *O. sanctum* were reported to have abortifacient effect in women (Batta & Santhakumari 1971). Ahmed *et al.*, (2002) had observed a reversible antiandrogenic property of *O. sanctum*. The extract of *O. sanctum* leaves made with benzene were issued to the albino rats for 48 days and it was reported that the sperm count and mobility as well as their forward velocity remarkably decreased along with reduced fructose levels.

Immunologic activity:

The findings from the study of treatment of methanolic and aqueous extract of *O. sanctum* leaves extract on albino rats revealed its immunostimulatory potentiality, acting by increasing the antibody levels in response to *Salmonella typhosa* and sheep erythrocytes (Godhwani, Godhwani & Was, 1988). Similar immunomodulatory effects were reported by Mediratta, Sharma & Singh (2002) with the treatment of seed oil of *O. sanctum* on rats while studying the humoral immune response.

Antistress activity:

O. sanctum have been reported to exhibit antistress properties and have the evidences of its usage in an extensive form in the Indian native system of medicine for various types of disorders related to anxiety. Administration of the 70% alcoholic extract of *O. sanctum* using ethanol controlled the alternation in neurotransmitter level and reduced the stress due to noise, as examined on Wistar strain albino rats (Ravindran *et al.*, 2005).

Similar study on rats by Jothie Richard *et al.*, (2016) had found *O. sanctum* to be effective in management of stress effects by inhibition of cortisol release.

Ocimumosides A and B and ocimarin, are the three compounds that were extracted and isolated from the leaves, by Gupta *et al.*, (2007) along with other known compounds like apigenin. They reported the promising antistress effects of the first two compounds by normalizing hyperglycaemia, plasmacortisterone and adrenal hypertrophy.

Memory enhancer activity:

The efficacy of the extract of this plant as a neuro enhancer or cognitive memory enhancer agent have been studied in mice by Joshi and Parle (2006). The amnesic effect caused by scopolamine and memory deficit due to aging in mice could be mitigated by using the water-based extract of the whole dried plant. Alzheimer's disease and dementia among other disorders could also be treated similarly and have been found to show effective results.

Cardio-protective activity:

Cardiac endogenous antioxidants have been augmented and myocardial infarction could be prevented by the leaf extract of *O. sanctum*, being issued orally in rats, as reported by Sharma *et al.*, (2001) and Sood *et al.*, (2005).

Wound healing activity:

Several studies showed wound healing property of *O. sanctum*. Alcoholic extract of the plant using ethanol was investigated for treating lesions and wounds, as examined in albino rats; epithelial cell formation and the recovery rate through contraction of the wound was significantly increased (Shetty, Udupa & Udupa, 2008).

The consistent elevated production of tumour necrosis factor (TNF- α) was achieved by *O. sanctum* treatment and thereby healing of wounds were much earlier than usual (Goel *et al.*, 2010).

Larvicidal activity:

Eugenol and a triglyceride -1,3-dilinoleoyl-2-palmitin, from *O. sanctum* had shown larvicidal activity on the larvae of *Aedes aegypti* (Kelm & Nair 1998). The leaf extracts of *O. sanctum* were also found to induce larval mortality against *Culex quinquefasciatus* along with *Aedes aegypti* (Anees, 2008).

CONCLUSION

The tremendous pharmacological activities and a wealth of available literature make *Ocimum sanctum* one of the most valuable herbs in the plant kingdom. The pharmaceutical activities of the herb results from the amalgamated and synergistic interactions of the different phytochemicals present. This widespread herb is easily available in India and other neighboring countries, growing both in wild and cultivated forms. The extensive range of the properties of its chemical constituents makes it a potential entity for more detailed clinical research. More investigations will establish the prospects of using the plant and its active novel chemical constituents in a large scale in modern medicine.

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Investigational Treatment of Covid-19

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ABSTRACT

Coronaviruses are the primary cause of illnesses such as acute viral nasopharyngitis, severe acute respiratory syndrome (SARS), in addition to Middle East respiratory syndrome (MERS). The world was introduced to a novel coronavirus in 2019, which caused an outbreak in China's Wuhan area. This was identified as coronavirus 2 (SARS-CoV-2) which causes the infectivity known as COVID-19. This review is usually thought to be what medical pharmacists and therapists are most likely to encounter when considering experimental drugs in practice.

Keywords: Corona-virus; SARS CoV-2; COVID-19; Clinical Trials; Remdesivir; Favipiravir; Hydroxychloroquine; Lopinavir; Corticosteroid; Interferon's

INTRODUCTION

SARS is a newly discovered coronavirus. CoV-2, also recognized as COVID-19, is a new coronavirus strain that causes illness. The WHO announced in March 2020 that a broader worldwide trial called 'Solidarity' should be conducted to evaluate local level of facilities and care with one of the subsequent treatments: remdesivir, favipiravir, hydroxychloroquine, lopinavir, corticosteroid, and interferon's (Wang *et al.*, 2020). This review is usually thought to be what medical pharmacists and therapists may meet in practice while considering these investigational drugs (Zumla *et al.*, 2016).

REVIEW LITERATURE AND DISCUSSION

Medicines which are currently being accelerated through clinical trials

Remdesivir:

The first medicine licenced by the US Food as well as Drug management to deal the SARS-CoV-2 virus was Remdesivir. It has a strong link to the therapy of COVID-19 disease in hospitalised adults and children weighing more than 40kg aged 12 and up (University of Liverpool). COVID-19 therapies: connections and experiments (2020).

Mechanism of action:

Remdesivir is an adenosine analogue that binds to nascent viral ribonucleic acid (RNA) chains, forcing them to terminate prematurely and put a stop to virus replication. It is extensively spread throughout the human body in addition to is primarily removed by the kidneys (Wang *et al.*, 2020).

Clinical trials and studies:

In February 2020, Gilead Sciences started two stage three medical trials to ensure and analyse the security as well as efficiency of remdesivir in people with COVID-19. In a stage three randomised, double-blind, placebo-controlled, multi-center research, the efficiency and security of remdesivir in hospitalised patients along with very few to moderate COVID-19 respiratory syndrome were first assessed (US National Library of Medicine). COVID-19-2020). Remdesivir-based trial in patients with few to moderate COVID. The 2nd stage three trial will be a multi-center, randomised, double-blind, placebo-controlled test to ensure and assess the efficiency and security of remdesivir in

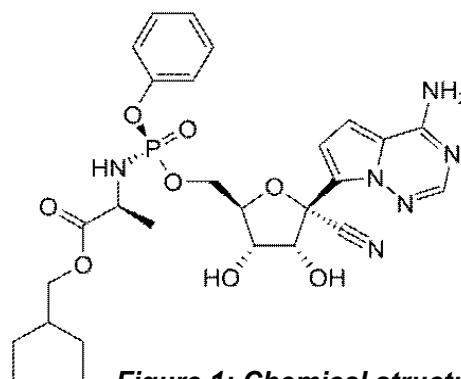


Figure 1: Chemical structure of Remdesivir

hospitalised patients along with severe COVID-19 respiratory disease (US National Library of Medicine). Adults with severe COVID-19-2020) are being tested with Remdesivir. Adults were the only ones who could participate in the trials. The patient received a well-continued standard of care and therapy (based on unspecified criteria) as well as remdesivir 200mg on day 1, followed by a 100mg once daily dose for 9 days, depends on which support of the research the patient was allocated to. Despite the fact that the experiment's three-month completion target of early May 2020 was overly optimistic, the trial was cancelled in April 2020 due to a shortage of qualified patients.

Remdesivir is currently being used successfully in the United Kingdom, and it has been studied in clinical trials all in excess of the world and in Europe. The primary is the Adaptive COVID-19 Treatment Trial (ACTT), which has enrolled over 1000 patients internationally plus is run in the UK in addition to EU by the Medical Research Council Clinical Trials Unit and University College London (UCL). On April 19, 2020, the UCL-led section of the trial stopped to fresh enrolment after enrolling 79 patients, 46 of whom were from the United Kingdom. In COVID-19 patients, the high-level findings demonstrated a progressive decrease in recovery time. As a result, the US Food and Drug Administration (FDA) has approved remdesivir for patients with severe COVID-19 who are hospitalised (US Food and Drug Administration, 2020).

Safety and practical consideration:

Remdesivir showed no effect on renal function in patients with Ebola virus syndrome in a repeated dose study. Remdesivir should be utilised with concern in patients with renal injury since it contains sulfobutylether—cyclodextrin, a solubilizing agent. Both Gilead phase three trials exclude patients with brutal liver sickness (e.g., Child-Pugh score C, AST > five times upper limit) as well as/or extreme renal impairment (e.g., estimated glomerular filtration rate 30ml/min/1.73m²), as well as those on continuous renal substitute therapy, hemodialysis, or peritoneal dialysis (Wang *et al.*, 2020). Carbamazepine, phenobarbitone, phenytoin, primidone, or rifampicin should not be taken with Remdesivir since these medications are enzyme inducers and can lower the medicine's blood plasma concentration.

Gilead has increased supply and production of remdesivir on many occasions to meet the need for using COVID-19 trials.

Favipiravir:

In COVID-19 clinical studies, favipiravir cleared the virus faster than lopinavir/ritonavir. Favipiravir has shown promising consequences in medical trials in China, Russia, and Japan, and multiple trials in the United States, the United Kingdom, as well as India are presently underway. Treatment guidelines have recently been implemented in a number of nations, and several Indian states have already included favipiravir in their treatment regimens. The key principle of this analysis is to provide insight into the evidence and evolving role of favipiravir in the treatment of COVID-19 infection, with an emphasis on the benefits of starting antiviral therapy. Favipiravir, its pharmacodynamics, pharmacokinetics, in vitro, medical data, as well as enclosure in COVID-19 therapy practices will be the subject of this (Delang *et al.*, 2018).

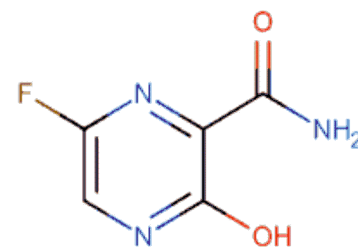


Figure 2: Chemical Structure of Favipiravir

Machinery of Practice:

Favipiravir (pro drug) is a purine analogue that is transformed into the active favipiravir ribofurabnosyl-5B-triphosphate (favipiravir-RTP) by a process known as intracellular phosphoribosylation. Its role is to act as a discriminating and powerful inhibitor of RNA viruses' RNA-dependent RNA polymerase (RdRp). Favipiravir is included into the embryonic viral RNA via the error-prone viral RdRp, resulting in chain extinction and viral mutagenesis. The mutagenic nature of favipiravir-RTP causes coronavirus repair machinery to flee, putting further strain on the Covid-19 nucleotide content. Because favipiravir

has a high affinity for the RdRp complex, it is used to target SARS-Achilles CoV-2's heel (Furuta *et al.*, 2017).

Clinical Trials:

Numerous open-label control studies and laboratory tests on various Chinese patients revealed that favipiravir had a shorter viral clearance time. It also demonstrated that the group with viral permission within 7 days of treatment had a good improvement rate on chest imaging (CT). Multivariate logistic regression revealed that the antiviral favipiravir is separately effective in improving chest imaging. Favipiravir was found to be responsible with quicker viral clearance using Multi Cox regression. Several other clinical trials have shown that favipiravir has a higher level of tolerance than Lopinavir/Ritonavir (Cai *et al.*, 2020).

Safety and practical consideration:

Favipiravir has been tried and tested over 4000+ patients showing positive results. The common adverse effects of favipiravir are downfall of neutrophil count, elevation of uric acid, elevation of SGOT and SGTP. Favipiravir is contradicted in expecting and lactating women because of its teratogenicity possible observed during animal reviews. In addition, favipiravir has been shown to be ineffective in patients with extreme Liver impairment, hypersensitivity, or severe kidney impairment. In patients with a history of gout, it should be given with caution. Favipiravir is the first antiviral oral medicine to be accepted for the mild and moderate treatment of Covid-19 patients. Favipiravir has been demonstrated to be a positive and potential cure for this disease in various studies conducted in China, Japan, and Russia (Zhao *et al.*, 2015).

Lopinavir and Ritonavir:

Mechanism of action:

Lopinavir and ritonavir work by preventing HIV and coronaviruses from replicating by inhibiting the protease enzyme. Ribavirin, a artificial nucleoside analogue, was used in conjunction with lopinavir and ritonavir and was found to be effective against the viruses (Electronics Medicines Compedium, 2020).

Clinical trials and studies:

Young *et al.* employed Lopinavir/Ritonavir to treat 18 patients in Covid-19 in Singapore at diverse doses to better understand their medical course. Lopinavir/Ritonavir was used to treat five of the eighteen patients. The results were unsatisfactory due to the small number of patients that took part. (Young and colleagues, 2020)

Safety and Practical consideration:

The synergistic powers of Lopinavir-ritonavir and ribavirin are poorly understood. As a result, there is a scarcity of specific knowledge regarding the combined treatment's mechanism of action. Anemia, angioedema, diarrhoea, dry mouth, dizziness, increased infection rate, and some anomalies in menstrual cycle are among side effects of Lopinavir-ritonavir. (British National Formulary, Lopinavir, 2017; Cao *et al.*, 2020).

Hydroxychloroquine sulphate:

The oral medication hydroxychloroquine is used to treat malaria and other inflammatory diseases. Hydroxychloroquine decreases the cytokine storm by decreasing T cell activation, and thereby

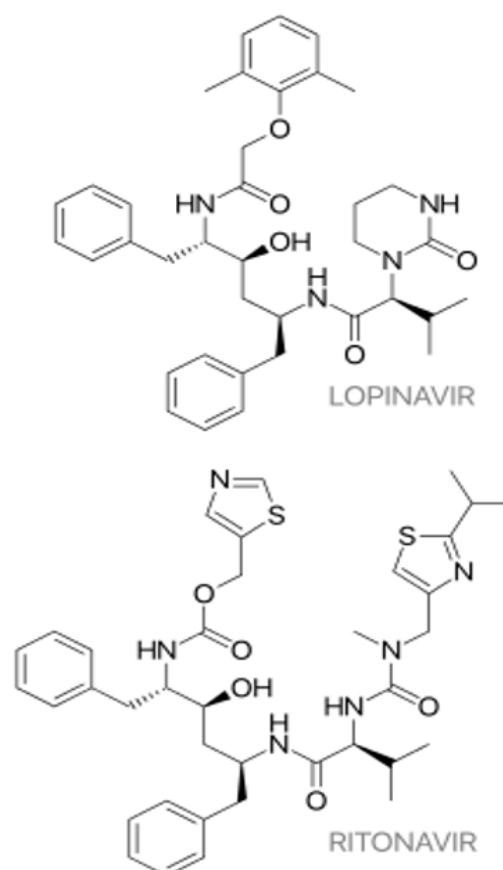


Figure 3: Chemical structure of Lopinavir-Ritonavir

CONCLUSION

Several Covid-19 medicines are being used un-licensed due to pandemic; for that reason, a long term data were needed for a proper evaluation in their efficiency and safety. So this review is about a detailed investigation of several possible treatment of covid-19, which can guide pharmacist and therapist in the time of pandemic.

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The Story of Aspirin: - Journey From Willow to Wander Drug

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ABSTRACT

The cheapest and most frequently used drug in medicine is Aspirin. In the wide range of pharmacological area, it is a non-steroidal anti-inflammatory drug, including antipyretic, analgesic, and antiplatelet assets. Aspirin has lengthily been hooked up as a beneficial analgesic and antipyretic. Even in historical times, salicylate-containing flora inclusive of the willow had been typically used to alleviate ache and fever.

Keywords: Aspirin; NSAIDs; Efficacy; Adverse Effect; History of Aspirin

INTRODUCTION

The trade name of Aspirin is acetylsalicylic acid created by the Bayer laboratories. The registered trademarks of Bayer laboratories are using some countries and some countries are using generic name of this substance. The most cost-effective in low doses medicine is Aspirin uses for the remedy of secondary measures of thrombosis. The Aspirin has great history from the ancient era, 2500 BCE it has used as herbal medicine, around 4000years ago Sumerian has used as medicine like clay tablets again Egyptians explain the use of willow leaves for inflammation or joint pain. Professor Johann Andreas Buchner purified salicin at the University of Munich from willow bark, in 1828. The chemical structure of salicylic acid was first worked out by Scientist Hermann Kolbe at Marburg University and a doctor, Thomas MacLagan recorded clinical trial of salicylate in 1876 to obtain complete decrease of joint inflammation and fever. Now the maximum commonly used drug around the Globe is Aspirin because it can prevent cardiovascular and cerebrovascular deasease also it is the most vital pharmaceutical fulfillment memories of the last Century. [PubMed review and texts: "Aspirin: The exceptional Story of a surprise Drug" (Jeffrey's 2005), and "The NSAID Wars: cash, Medicine, and 100 Years of Rampant Competition." (Mann & Plummer 1991)].

REVIEW LITERATURE AND DISCUSSION

Historical Improvements study of Salicylates

Edwin Smith, in 1862, did one a few of the maximums traditionally critical acquisitions of his existence. Well regarded among his buddies for his keen supply and intricate know-how of Egyptology, he Smith obtained, for £12, 2 worn paper rush scrolls throughout a close-by Luxor Avenue market¹ that later grew to grow to be bent be a influential medical manual exposing ancient Egyptian's workout of medicine. Though authorless, the Ebers Paper rush is 110 pages and brought into attention the maximum whole medical paper rush ever improved; it dates come in to 1534 BC. It covers a giant type of medicinal situation and ≈seven-hundred pharmaceutical and herbal remedies; however the maximum crucial plant species said is tjeret or Salix, regarded these days as willow tree. The Ebers Papyrus illustrates the using of this tree, which is grow in most additive of the primitive world, as each a general-motive tonic or an anti-inflammatory/pain reliever for nonspecific aches and pains. Via this trade by 216 AD, navy contacts, and neighboring coastal metropolis communications, willow had locate yourself a commonly used remedy in the course of the civilized world. Many years later, in 1758, Respected Edward Stone fed on the bark of an English willow.¹ and try to discover an effective and a long way much less highly-priced remedy for "the agues" (now seemed to be malarial signs:

fever, myalgias, and headache), Stone administered ground-up dehydrated willow to ague victims and showed that the substance modified into, in fact, effective in treating the ones signs. The dawn of the nineteenth century grows to be marked with significant exchange in terms of technological innovation, clinical inquiry, and economic prosperity. The first widespread discovery within the race to grow to be aware of and synthesize the energetic factor of willow came from Joseph Buchner, a professor of dispensing chemists at Munich University who, in 1828, sensitive willow into yellow crystals and labeled it salicin (after salix, Latin for willow). The French pharmacist Henri Leroux in addition sensitive the salicin extraction procedure in 1829, handiest to be outdone via way of means of Raffaele Pieria who produced a more potent composite from the crystal that he aptly named 2-hydroxybenzoic acid in 1838.

The use of salicylate medications a few years of the 19th century, which blanketed salicin, 2-hydroxybenzoic acid, grew significantly, analgesic and physicians a developing wide variety of knew what to expect clinically from the ones medicines: markdown of ache, fever and inflammation. Inappropriately, the ugly component consequences, in particular gastric irritation, restrained their usefulness, and attempts to pass the ones untoward consequences were unsuccessful until Ferdinand Runge observed the compounds aniline and phenol within the residue left inside the returned of at the same time as burning coal (coal-tar). Runge's discovery, on the aspect of Henry Perkins' go after coal-tar-derived dyes, gave upward thrust push to the herbal chemical enterprise and might later play a huge function within the improvement of aspirin.

Charles Gerhart at Montpellier University, a professor of chemistry by 1852, concluded that the molecular kind of 2-hydroxybenzoic acid contained of a treasured benzene components with 2 related hydroxyl and carboxyl components. By converting the hydroxyl affiliation with an acetyl organization, Gerhardt have emerged as the primary man to chemically manufacture aspirin. Inappropriately, Gerhardt's compound grew to become bent be adulterated and volatile and attracted no in addition importance. The first exact medical test regarding salicylates is accredited to John Maclagan. Maclagan managed salicin to sufferers with rheumatism., Maclagan's test out positioned that the one patients who acquired salicin experienced a remission of fever and joint inflammation which is published in *The Lancet*.

The first meticulous scientific trial regarding salicylates is accredited to John Maclagana. A Dundee Royal Infirmary physician, Maclagan, administered salicin to sufferers with rheumatism. Maclagan's look at located that the ones sufferers who obtained salicin skilled a remission of fever and joint inflammation which is also published in *The Lancet*.

Eichengrün did not get hold of the refusal from the apex of the medicinal drug branch and forced earlier to run his very own scientific trials, alongside drug is taken by himself about the disagreement over the invention of aspirin. These types of trials passionate to modify it into a powerful anesthetic and had no evident harmful consequences on the heart. Dreser modified into now not stimulated and composed a legendary be conscious within side the boundary of Eichengrün's file: 'It is the identical antique Berlin boasting (Jeffreys, 2004). Still, after the involvement of the top of the part who prepared in addition experiments and the medicine can be manufacture expected by Dreser.

Aspirin modified into granted thru manner of approach of a team who had tested the drugs. The name modified into advanced from a combination of spiraea and acetyl. Even though the utility of aspirin within the clinical society modified into to begin with time-consuming, it fast took off and aspirin surprisingly have emerge as appeared international as one of the preliminary ache relievers. Even though Eichengrün and Hoffmann completed no fees for the improvement of aspirin, Dreser modified into rewarded credits on each treatment in his research laboratory and labored without delay to create a private wealth from the expansion of aspirin (Jeffreys, 2004). Even though Felix Hoffman is broadly recounted with the finding of aspirin, here may be various controversies around his announce (Sneader, 2000). Bayer modified into producing massive numbers of new pills at the time of discovery and no character changed into accredited with the innovation. In 1934, it is modified; files of discovery

of aspirin were written by Schmidt after looking during the Bayer records (Schmidt, 1934). Particularly, Eichengrün's effect to the innovation modified into overlooked.

Eichengrün modified right into a Jew and the upward thrust of the Nazi can also moreover have restrained to make a announce to a function. He had, thru manner of approach of this period, went Bayer to build his very own enterprise agency but modified into challenged with sturdy policies on his artwork. In 1938 he modified into pressured to sell his commercial agency and in 1944 he modified into dispatched to the Theresienstadt awareness camp wherein he continued until the Russians launched it in 1945 (Sneider, 2000).

After 15 years, in 1949, the book of the file credit score to the invention to Arthur Eichengrün, Hoffmann, written a paper highlighting the artwork modified into executed beneath his route. He moved without delay to component out that he detected acetylsalicylic acid due to the fact the remarkable compound that they had separated and modified into primary name for scientific trials. He recommended he had experience it on himself and have begun out the primary trial run. These type of trials hooked up the anaesthetic consequences and antipyretic of acetylsalicylic acid further to its beneficial aspect impact report (Eichengrün, 1949).

Higher push of aspirin

The aspirin is release within 3 years into the marketplace; admiring the qualities of aspirin over 160 medical papers is published. It worked without delay to come to be relatively a achievement spherical the area. Following World War-I, in 1918, the area modified into strike through manner of approach of each different disastrous event, a universal outburst of infection. About 50 million humans passed from the epidemic: extra than passed from stopping within side the entire of World War-I (Shanks, 2014). There is no remedy is probably located, and vaccination end up unsuccessful. Aspirin have end up extensively used and modified into successful in alleviating the symptoms and symptoms of influenza, even though it modified into now now not effective in decreasing mortality. Its acceptance modified into sustained subsequently and aspirin went without delay to be considered through manner of approach of the overall community and the clinical occupation as a active febrifuge and analgesic, with limited issue results even as taken at present day doses (Lancet Editorial, 1935).

Aspirin gradually plunges not in of benefit

Aspirin professional some of barriers over the subsequent days. In 1932, at the back of the breakthrough of the gastroscope it speedy has become noticeable that aspirin advantage grow to be correlated with gastritis (Douthwaite & Lintott, 1938, Douthwaite, 1938;). The improvement of recent anaesthetic entrepreneurs with out the ones issue effects, together with ibuprofen in 1962 and paracetamol in 1956, similarly dented aspirin's popularity. In addition, troubles had been recognized in 1962 even as aspirin end up advised to be correlated with Reye disorder in teenagers (Mortimer, 1962). This instance is said to a excessive brain disorder and fatty penetration of the intestines and need to be lethal. All over the subsequent years, there was increasing proof for this institution (Linnemann *et al.*, 1975) and aspirin isn't exemptions for anyone beneath sixteenth years, however there are some exceptions, like remedy of Kawasaki disorder. Nobel Prize presented for records how aspirin struggled even as aspirin emerge as a reasonably a success product, little become into appeared in relation to its method of achievement. This began out out to come to be fairer later withinside the nineteenth century as systematic enhanced. maximum important manuscripts hypothesizing how aspirin struggled turn out to be posted in 1960 thru Collier & Shorley (1970) and Harry Collier (1912–1983), a pharmaceutical business organisation modified into strolling with the resource of using a scientist for Allen and Hanburys. He managed the bradykinin to avoid bronchoconstriction of Aspirin in guinea pigs with the useful resource of the use of following element. Aspirin did presently now not exert an impact if it grow to be given even as bradykinin, critical him to hypothecate that Aspirin repressed bradykinin. Priscilla Piper, in 1963 (d. 1995), a PhD pupil from the London university, attached Harry Collier to artwork on the method in the lower again of the consequences of aspirin. They driven earlier with experiments for the following 5 years however

struggled to shape similarly inroads. In this factor, Collier suggested that Piper want to be part of John Vane's laboratory as a postgraduate pupil to investigate fresh experimental techniques and to require the studies of the mechanism of aspirin additional. He (1927–2004) may be a solution decide withinside the facts of aspirin. In 1927, he have emerged as born in Birmingham, uk and went on to check out chemistry at the college of Birmingham in 1944, in advance than than shifting to the college of Oxford in 1946 to take a look at pharmacology. The university of Sheffield directly accept him and Yale withinside the us earlier than he another time to the UK to artwork withinside the college of London in 1955 in which he advanced the 'blood-bathed appendage cascade'. It becomes a way into a method wherein blood emerge as into handed over tissue strips. The number one 'upstream' strips become treated to line off it to launch of cytokines. He wishes to then take a glance on the results on the down easy strength to appear if it gotten smaller in return to the cytokine that turn out to be launched. He applies the method to vigorously diploma stages of blood hormones, which include angiotensin and bradykinin (Flower, 2005). Priscilla Piper labored with John Vane the use of this approach to take a look at how aspirin interacted with first-rate cytokines. They were the use of a version of the blood-bathed organ cascade wherein rabbit aorta changed into used because of the fact the 'downstream' tissue. They show off that aspirin antagonized an unidentified cytokine that they named 'rabbit aorta astringent component'. They went directly to repeat Collier's experiments as an example that injecting rabbit aorta contracting issue into the guinea pig induced anaphylaxis which modified into antagonized thru way of way of aspirin (Piper & Vane, 1969). Vane emerge as capable of circulate on for example that rabbit aorta contracting aspect come to be a prostaglandin which inhibited its synthesis (Vane, 1971). The expression that the aspirin inhibited prostacyclin production covered the way for the prospect improvement of anti-inflammatory tablets (NSAIDs) and considered one of a kind cyclooxygenase (COX) enhancer and in 1982, gained John Vane the Nobel Prize for body structure or medicinal drug. In 1984, he also knighted and went devoid of delay.

Application or uses of Aspirin

Treatment and Prevention of cardiovascular disorder: -

Primary prevention: -

The advantages of aspirin remedy for the secondary prevention of cardiovascular disorder truly outweigh the dangers of bleeding, and coffee-dose aspirin is uniformly endorsed on this setting. However, no clean consensus exists approximately whether, and in that case in whom, aspirin remedy is suitable for the number one prevention of cardiovascular disorder. Three trials of low-dose aspirin as opposed to placebo in 3 populations at multiplied threat of myocardial infarction or ischemic stroke withinside the absence of hooked up cardiovascular disorder had been suggested in 2018. The ASPREE trial in aged human beings changed into terminated early for futility due to the fact aspirin had no impact on disability-loose survival however appreciably multiplied the threat of most important haemorrhage and, unexpectedly, all-reason mortality. In the ASCEND trial in sufferers with diabetes mellitus and no proof of vascular disorder, aspirin appreciably decreased severe vascular occasions however multiplied most important bleeding. In the ARRIVE at trial in human beings with more than one threat elements for cardiovascular disorder, aspirin had no impact on most important cardiovascular occasions however multiplied gastrointestinal bleeding. The intention of this Review is to location those new effects withinside the context of preceding proof on aspirin for the number one prevention of cardiovascular disorder and to appraise whether or not the brand-new proof is probable to allow the greater focused use of aspirin specifically people for whom the internet gain is each clinically profitable and statistically definite.

Secondary prevention: -

Patients who be afflicted by one or greater CVD occasions, inclusive of myocardial infarct (MI) or ischaemic stroke, are at very excessive threat for each other CVD event. While rescue procedures, inclusive of percutaneous coronary intervention (PCI), are geared toward stabilizing acute occasions,

aspirin remedy may additionally in reality serve to save lots of you next CVD occasions. The position of aspirin in lowering CVD mortality and repeat occasions after acute MI become first established withinside the 2d International Study of Infarct Survival (ISIS-2) trial.⁷ during this check out, 17,187 sufferers from 417 hospitals had been enrolled inside 24 hours after onset of suspected acute MI and randomized to receive: (i) one month of one hundred sixty mg/day enteric-lined aspirin; (ii) a 1-hour intravenous infusion of 1.5 MU of streptokinase; (iii) each treatments; or (iv) neither. Aspirin use led to a large discount in non-deadly reinfarction, stroke, five-week vascular mortality, and all-reason mortality. Although different, smaller trials confirmed comparable advantages for sufferers with a record of preceding MI, the ISIS-2 trial become the first to supply proof of an instant impact of aspirin on acute MI, demonstrating that one month of low-dose aspirin commenced directly after MI in one thousand sufferers might prevent 25 deaths and 10 to fifteen nonfatal infarcts and strokes. Additional mortality advantages had been located with longer length of aspirin remedy. Since the ISIS-2 trial, many various organizations have established comparable effects while aspirin is used for secondary prevention of CVD occasions. In 2002, the Antithrombotic Trialists' Collaboration analyzed sixteen trials of lengthy-time period aspirin use with doses ranging from 50 – 1500 mg/day for secondary prevention of CVD occasions, alongside over 17,000 topics and three,306 severe vascular occasions. In those trials, aspirin use led to sizable discounts in severe vascular occasions alongside stroke and coronary occasions in each woman and men and coffee dose regimens (75 – 100 mg/day) had been located to be as powerful as better doses. A 2020 booklet searching on the secondary prevention of cardiovascular disorder has proven that aspirin continues to be one among the good options.

Aspirin in most cancers' prevention and management

1988 Professor Gabriel Kune observed that human beings taking aspirin had a 40% decrease threat of growing most cancers of the huge. Other studies have similarly supported this locating and a time established decreased prevalence in colorectal most cancers has been located. In 2011, Sir John Burns confirmed the position of aspirin in supporting to save you most cancers in vendors of hereditary colorectal most cancers. Further research is ongoing to absolutely apprehend aspirins position in most cancers' prevention along with the position of aspirin in lowering the threat of meta static spread in hooked up most cancers.

Primary disorder prevention: -

Result from current number one prevention trials inclusive of ASCEND, ASPREE, ARRIVE, Aspect's seafood etc. have precipitated loads of dialogue and discussion²⁶ and brought on refinement of similarly studies research. It is turning into obvious that an individualized technique is crucial in addition to cautious attention of age and all threat elements. Individualized dosing regimens may be had to absolutely take advantage of the probable lifesaving advantages of this captivating drug. A one length suits all technique isn't always suitable and elements inclusive of multiplied platelet turnover in sure disorder situations e.g., diabetes leads to 'unblocked' platelets withinside the stream while a as soon as everyday aspirin regime is used, similarly frame weight can outcomes aspirin effectiveness.

CONCLUSION

Aspirin, and especially Low-dose Aspirin, has a therapeutically capability away from its previously regarded outcomes inside the anticipation of numerous sicknesses together with myocardial infarction, atherothrombotic events, strokes and colon cancer. Except the pharmacological outcomes that it shares with different NSAIDs can induce other lipid-derived mediators with effective stimulation and anti-inflammatory actions of the resolution of irritation places aspirin in a privileged function in the therapeutic arsenal. This review is a deep observe of the molecular mechanisms indirect inside the outcomes of aspirin and of AT mediators to suggest a extra lucid use of it based totally on the choice of sufferers who should gain from aspirin, when the remedy should begin, and the dose that need to be apply.

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Cisplatin: The Most Widely Used Anticancer Drug

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ABSTRACT

Cisplatin or cis-diamminedichloridoplatinum(II) is one of the most successful and efficient chemotherapeutic drugs for the treatment of various types of malignancies, including bladder, testis, ovary, head and neck, lung cancer, germ cell tumors, lymphomas, sarcomas, and many others. Cisplatin molecules bind with DNA to form an adduct which finally transduces several signalling pathways, resulting in apoptosis and cell death. Unfortunately, neither cytotoxicity nor apoptosis are completely generated in cancer cells, therefore cisplatin may have a variety of side effects that limit its use and effectiveness. The restoration of cisplatin's efficiency is a difficult task for medical science. Combination therapies, in which other anticancer drugs containing platinum are used in combination with cisplatin in chemotherapy treatment, are being utilised to reduce cisplatin resistance and side effects, and have become successful in overcoming drug resistance and reducing toxicity. This article mainly highlights the brief description of cisplatin as an anticancer drug. This article briefly describes the first innovation of cisplatin, its synthesis method, molecular cellular mechanism of action, its activity as an anticancer drug, and its side effects and resistance. Special attention is given to cisplatin, transplatin, and any other platinum drugs that are not properly addressed.

Keywords : *Cisplatin; Cancer Treatment; Drug Resistance; Side Effects*

INTRODUCTION

Cancer is the most severe health problem and the second leading cause of death (Ghosh, 2019; Siegel, Miller & Jemal, 2018). IRAC reported nearly 7.6 million cancer-related deaths worldwide, with 12.6 billion new cases reported each year (Baskar *et al.*, 2012). Cancer arises when abnormal cells in the body proliferate uncontrollably. Old cells do not die when the body's usual regulatory mechanisms fail, but new cell growth continues, leading to the formation of aberrant cells. These cells form a mass of tissue called a tumor. Cancer may be treated depending on the type. The first one is surgery, which directly removes the tumor, but it is only possible if the cancer is localized. Radiation therapy using X-rays is a way to damage cancer cells. Chemotherapy is an efficient and widely used way to kill cancer cells (Baskar *et al.*, 2012; Shewach & Kuchta, 2009; Eastman, 2017). Cisplatin is one of the most potential and widely used first-generation metal-based chemotherapeutic agents (Siegel, Miller & Jemal, 2018). It is reported that nearly 2 billion US dollars are invested in the platinum-based anticancer drug (Siafaca, 1999). From the studies, it is found that nearly 50% of patients are treated with cisplatin, which is effective at curing 90% of testicular cancer. It is more effective in the treatment of cancers like head and neck cancer, ovarian cancer, bladder cancer, cervical cancer, melanoma, and many more (Hambley, 1997). Though cisplatin is successful, it does not show its maximum efficiency due to its resistance and side effects, which are mainly due to protein binding (Ghosh, 2019). This is the reason that led researchers to develop a thousand cisplatin analogs, but only two have been approved (Wilson & Lippard, 2014). But most of the platinum complexes are less effective compared to cisplatin (Zhang *et al.*, 2010).

This review article is a brief overview of the drug cisplatin from its first to last. The synthesis method, its cellular mechanism, anticancer activity, side effects are also briefly encountered by this review. It should be noted that this review is only centred on cisplatin; the other platinum complexes and their

properties are not incorporated into this article.

LITERATURE REVIEW

First innovation of metal based anticancer drug

Alfred Warner published 14 papers on platinum chemistry between 1896 and 1920 (Ghosh, 2019). In 1997, George B. Kauffman analysed Alfred Warner's platinum metals study, which disproved the Blomstrand-Josrgenses chain explanation for the formulation of the isomers cis and trans $[\text{PtCl}_2(\text{NH}_3)_2]$ (Wilson & Lippard, 2014). Michele Peyrone initially described the cis isomer $[\text{PtCl}_2(\text{NH}_3)_2]$ in 1844 and termed it "Peyrone's salt" (Peyrone, 1844). In 1893, Warner deduced the structure of the cisplatin complex. Warner assumed that the isomers which result in two different colours are mainly due to the cis and trans position of the ammonia and chloride ligands and derived a square planar geometry of cis and trans $[\text{PtCl}_2\text{NH}_3]$ (Constable & Housecroft, 2013). But the anticancer activity or inhabitation of cell division of cisplatin was accidentally discovered by biophysicists Rosenberg, Van Camp, and Krigas (1965). In a study of the effect of the electric field on the cell division in NH_4Cl buffer, Mr. Barnett noticed that the cells of the *E. coli* became long, and after a long study, he found that the phenomenon only occurred due to the inhibition of cellular division. Finally, it was proposed that cell division be restricted by a platinum compound released from the electrode. From these observations, the cisplatin Pt(II) complex was tested against sarcoma 180 tumours in Swiss white mice. The complex demonstrated potent activity in shrinking large solid tumors. After a successful journey with cisplatin, this drug is now the most potent in the field of cancer treatment.

Synthesis of cisplatin

In 1944, Michele Peyrone first synthesized cisplatin, though its structure was still unknown till that date. After 50 years, Alfred Warner proposed its square planar geometry and its isomers (Mellor, 1943). The early method of synthesis needed some improvements for better yield, purity, and reaction time. Dhara (1970) proposed a most important method for preparation of cisplatin. In 1970, Dhara described "A rapid method for the synthesis of cis- $[\text{PtCl}_2(\text{NH}_3)_2]$." In this method, the starting material $\text{K}_2[\text{PtCl}_4]$ is first treated with a saturated solution of KI to form the tetraiodo analogue $\text{K}_2[\text{PtI}_4]$. Then NH_3 is added to this tetraiodo analogue to form cis- $[\text{PtI}_2(\text{NH}_3)]$, a yellow compound. This yellow compound is now dried and an aqueous solution of AgNO_3 is added to it. After the addition of AgNO_3 , an insoluble precipitation is noticed which is nothing but the precipitation of AgI, which is filtered and discarded. After treating with KCl in the filtrate containing cis- $[\text{Pt}(\text{OH})_2(\text{NH}_3)]^{2+}$, a yellow powder product cis- $[\text{PtCl}_2(\text{NH}_3)_2]$ is obtained. (Davies *et al.*, 2008). Recrystallization with hot water containing 0.9% NaCl produces more purified cisplatin. The efficiency of this process is mainly dependent on the trans effect, which was first introduced in 1926 by Chernyaev (Basolo & Pearson, 1967). The incorporation of a second ammonia ligand into the intermediate triiodo species $\text{K}[\text{PtI}_3(\text{NH}_3)]$ may result in the substitution of an iodo ligand that is trans to another iodo group or the iodo group that is trans to ammonia, but the final cis product is obtained due to the strong trans-directing iodo group to the ammonia. Actually, the earlier process does not contain the initial step, which is the conversion of $\text{K}_2[\text{PtCl}_4]$ to $\text{K}_2[\text{PtI}_4]$. But this step only ensures that the final product is mainly a cis-oriented product (Alderden, Hall & Hambley, 2006).

DISCUSSION

Mechanism of action

It is beyond the scope of this article to elaborately explain the molecular cellular mechanism of cisplatin as an anticancer drug. This review presents a brief description, more particularly, an overview of the mechanism of cisplatin activity. Generally, cisplatin exposes its anticancer activity by binding to DNA (Ivanov *et al.*, 1998). Cisplatin intravenously administered to a patient as a sterile saline solution (Ghosh, 2019). Many studies indicate that cisplatin primarily interacts with proteins

that contain a thiol group, such as the amino acid cysteine, human serum, and albumin. It should be noted that protein binding accounts for 65 to 98 percent of the platinum found (Ivanov *et al.*, 1998). This protein binding has been bound by its drug activity, and some serious side effects have developed from this binding. The unbound remaining cisplatin can enter the tumour cells by cell membrane diffusion (Gately & Howell, 1993). But some studies suggest that Cu transporting proteins are factors for the transportation of cisplatin across the cell membrane (Ishida *et al.*, 2002). Once the cisplatin enters the cell, its exit is restricted by forming a reactive, positively charged species. As the chloride concentration inside the cell is lower, one of the chloride ligands of cisplatin is replaced by water and hence the reactive species is formed (Davies, Berners-Price & Hambley, 2000). This mono-aquated reactive species can efficiently form platinum binding to DNA within the cell nucleus at least 98% of the platinum (Davies, Berners-Price & Hambley, 2000). This monofunctional DNA adduct is mainly formed by binding with guanine, which is one of the DNA bases. To form a bifunctional adduct, the ring closure may occur either directly from the monofunctional DNA adduct or by aquation of the second chloride ligand present in cisplatin (Jamieson & Lippard, 1999). At the primary stage, the bifunctional adducts are mainly guanine–guanine types or adenine–guanine types (Cohen *et al.*, 1980). The bifunctional adducts result in a severe distortion of the DNA molecule, which can be easily acknowledged by DNA-binding proteins. These binding proteins may initiate DNA repair or they may be the cause of cell death (Guo & Sadler, 1999).

Use of cisplatin for cancer treatment

Use of cisplatin for treatment of lung cancer

Lung cancer is one of the most common fatal diseases. Chemotherapy is the most effective treatment for small cell lung cancers (SCLC), as these tumours are generally widespread when diagnosed. The two most important drugs are cisplatin and carboplatin that are used in SCLC chemotherapy. Nevertheless, cisplatin is chosen over carboplatin due to its strong antitumor activity, though it can cause side effects including renal nausea and vomiting. Chemotherapy, along with radiation therapy, is most effective for patients with stage III and stage IV lung cancer that cannot be surgically removed (Zappa & Mousa, 2016).

Use of cisplatin for treatment of ovarian cancer

Ovarian cancer is one of the most common forms of cancer in women, leading to highest death. Even though the exact cause of ovarian cancer is unclear, it can be expected in people with breast or colon cancer and because of inadequate screening strategies and specific symptoms of early-stage disease to detect it. Cisplatin is the most effective treatment of ovarian cancer as a chemotherapy agent although it has several side effects. Therefore combination therapy is used for better treatment as there is a chance to reappear in future (Kakar, Jala & Fong, 2012).

Use of cisplatin for treatment of testicular cancer

Testicular cancer is a great concern for young men as seminoma and non-seminoma, two types of it, are generally seen among them. Cisplatin-based chemotherapy is the best for the treatment of seminoma testicular cancer. 85% of patients are cured with the help of cisplatin after three or four cycles. Non-seminomas are generally seen after their late teens. There are four main types of non-seminomas: embryonal carcinoma, yolk sac carcinoma, choriocarcinoma and teratoma. Cisplatin, along with other chemotherapeutic drugs such as bleomycin and etoposide, is used in combination therapy, which is the most competent method of treatment for patients with teratoma. Many mechanisms are planned so that they can be explained clearly. Gong *et al.* (2010) demonstrated that prostate cancer cells more express Kindlin-2, which regulates the death of cancer cells. Usanova *et al.* (2010) found that cisplatin sensitivity in tumour cells in the testes.

Use of cisplatin for treatment of other cancers

Cisplatin is also widely used as a treatment for brain tumours in children, stomach cancer, leukemia

etc. It is very useful for the treatment of breast cancer patients as it makes hope to live long for patients. (Dentino *et al.*, 1978). In the case of squamous cell carcinoma of the head and neck (CCSSN), this therapy may not be effective although overall liability is good for the patients. Cisplatin really a brilliant chemotherapy agent that can be used for the treatment of different types of cancers that is severe to the patients (Tsimberidou *et al.*, 2009).

Side effects of cisplatin

Cisplatin is highly effective in treating testicular and ovarian cancer, although it has many side effects that may be seen by using an overdose of it. The main side effects of cisplatin have been mentioned below.

Nephrotoxicity

Nephrotoxicity is one of the most frequent kidney problems and happens when your body is exposed to a medication or toxin that causes damage to your kidneys. Renal toxicity has been noted when treated with cisplatin in the form of a single 50 mg/m² agent in 28% to 36% patients. This renal toxicity becomes severe when using drugs in a repeated manner. Nephrotoxicity is the cause of the increase in blood urea nitrogen (BUN) (Petrovic & Todorović, 2016). The risk of nephrotoxicity can be decreased due to intravenous hydration of at least 3–6L per day (Tsang, Al-Fayea & Au, 2009).

Ototoxicity

Ototoxicity is a major side effect for 31% of patients when they were treated with a single dose of 50 mg/m² cisplatin, and it also affects more children than adults (Petrovi & Todorovi, 2016). Hearing loss is caused by excessive use of cisplatin and has become more severe for adults. It is not clear whether the reversibility of the cisplatin-induced ototoxicity is complete. Hearing loss is typically in the high frequency range, bilateral, and permanent (McKeage, 1995). Deafness has also been reported as a side effect. Antioxidants and anti-inflammatory medicines must be administered locally or in a systematic manner to treat cisplatin-induced ototoxicity (Rybak *et al.*, 2007).

Hepatotoxicity

Hepatotoxicity can occur if you take too much cisplatin. This is mostly caused by oxidative stress, which is induced by an increase in transaminases and bilirubin in the bloodstream (İşeri *et al.*, 2007). Cisplatin treatment has also been shown to increase cytochrome P450 levels, and the cytochrome-P450-2E1 enzyme (Caro & Cederbaum, 2004). Hepatotoxicity can be reduced by taking large amounts of selenium and vitamin E (Liao *et al.*, 2008).

Gastrointestinal toxicity

Nausea and vomiting, abdominal pain, and a chemical hepatitis characterised by a disturbance of liver function enzymes are all symptoms of gastrointestinal poisoning. Despite routine preventive antiemetic therapy, almost all patients experience severe nausea and vomiting. There have also been reports of diarrhoea, loss of taste or metallic taste, pancreatitis, and mucositis (Tsang, Al-Fayea & Au, 2009).

CONCLUSION

Cisplatin is one of the most potent and effective anticancer drugs. Cisplatin can treat many types of solid cancers, which are already mentioned in this article. The general mechanism of action of cisplatin, which causes apoptosis by damaging DNA and inhibiting replication, is not the only way to describe its cellular mechanism. There are a number of mechanisms of action of cisplatin that have been proposed with evidence, but none of them can completely describe its cellular action. So it is obvious that it is a great area of interest for chemists and biologists to find its complete mechanism. The major challenges for cisplatin are toxicity, side effects, and drug resistance. This resistance and side effects mainly arise due to the binding of cisplatin with proteins and changes in cellular uptake. These side effects and resistance can be overcome by the combination of cisplatin with certain platinum agents. Combination therapy has become an efficient way to restore the efficiency of

cisplatin. Finally, combination techniques that reduce the uptake of cisplatin could offer the best clinical application of cisplatin.

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Ethnomedicinal Uses in West Bengal, India

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ABSTRACT

This study was focus to find out some ethnomedicinal uses in West Bengal which are used to treatment various disease through this traditional knowledge. This indigenous knowledge can used for human being. Folk people or ethnic group of people are our main source of indigenous traditional ethnomedicine. They use locally medicinal plants for their treatments. In this review, we discuss some medicinally important plants which are used as ethnomedicine.

Keywords: *Ethnomedicine; Medicinal Plants; Uses*

INTRODUCTION

Ethnomedicine is commonly known as traditional indigenous medicinal plants which are used by folk people or by ethnic group. Ethnomedicinal studies (Jain, 2017) are important for the study of new crude drugs from different indigenous medicinal plants. Due to lack of modern medicinal facility, bad economic condition they adopt indigenous ethnomedicine. This practice mainly found in rural population especially tribal community (Mondal, Paul, Hoque, 2015; Das & Ghosh 2017). They practice this ethnomedicine and inherit generation to generation. In India more than 3000 plant species are reported (Prakasha *et al.*, 2010) medicinal properties.

The term Ethnobotany was first introduced by Harshberger in 1876 which means 'the study of plants used by ethnic or ancient people'. Now a days ethnobotany means direct relationship between plants and human population. Indian region is one of the greatest center of ethnobotanical wealth and a store house of traditional knowledge. Most of the tribal people still live far away from the influences of the modern world and maintain close association with the medicinal plants for all their needs. Indian region supports a large biodiversity of ancient lineage. It provided unique opportunities for study of ethnobotany. It is a science dealing with relationship between human and plants (Mukherjee, 2003). Ethnobotany is a mixture of different discipline like Botany, Anthropology, Sociology and Culture, Language and linguistics, Religion and Social customs, Medicine, Mythology, Geography, Economics and a many other subjects.

All tribes have their own names for plants in the different regions. It may be seen that a single plant has different local names in different regions. So local names/vernacular names help in verification of the uses with other persons at a later date.

Plants are used in the traditional medicines for several thousands of years. In the ancient age the people used the raw plants as food for their nutrition and used the crude drugs for remedies. Charak Samhita (1000 BC-100 AD) has reported more than 1000 herbal remedies. Not only that, the holy Vedas also remind us about the traditional medicinal uses of various plants. Atharvaveda (around 1200 BC), Charak Samhita and Shusrut Samhita (1000-500 BC) are the source of our indigenous traditional detailed description of different herbs and describes the uses (Tripathi *et al.*, 2013). Ayurveda, Siddha and Unani are the evidence of the traditional medicines. During the last few decades, natural products are popular worldwide and known as herbal medicines. This practice of natural products actually is based on belief and experience of the ethnic people. However, this traditional knowledge doesn't have any written documents, they carry on orally generation-after generation and still accepted by around the world. In 77th A.D great Greek surgeon Pedanius Dioscorides published "De Materia Medica" which is a book of information about many plants used by ancient Greeks in medicinal purpose.

LITERATURE REVIEW AND DISCUSSION

Particular in human health care ethnomedicine has been playing very important role. In India ethnic people belief of their tradition and culture and they use as a health care practices (Ghosh, 2008; Chakraborty & Bhattacharjee, 2006; Sahoo & Sivaramakrishnan, 2014). These particular traditional medicines have no side effect as well as very effective, cheap and locally available. It also effects in international trade for its herbal drug demand and as a result ethnobotany is more importance for traditional medicinal knowledge like uses, preparations, doses and other important information regarding crude drugs. Now a days extensive research work done in the field of ethnobotany which help us to explore traditional knowledge. Folk traditional treatment procedure protocol, pharmacology, tribal medicine system is still not well known in different areas of West Bengal (Tripathi *et al.*, 2013, Rahaman & Karmakar, 2015).

Table 1: Some Important Ethnomedicinal Plants & Uses

Sl. No.	Plant Name (Local Name)	Scientific Name	Family	Habit	Parts Used	Uses
1.	Kalmegh	<i>Andrographis paniculata</i> (Burm. f.) Wall ex Nees	Acanthaceae	Perennial Herb	Whole plant, mainly leaves, roots.	Used loss of appetite; improve liver function and digestion; irregular stools. Used in fever, general debility, dysentery, dyspepsia.
2.	Nayantara, Chirabasanta	<i>Catharanthus roseus</i> (L.) G. Don	Apocynaceae	Perennial Herb	Entire plant	Plant parts used to cure diabetes diabetes mellitus), hypertension, leucorrhoea, leukemia. Latex also applied to cure cancerous wounds.
3.	Thankuni, Manduki	<i>Centella asiatica</i> (L.) Urban.	Apiaceae / Umbelliferae	Creeping Herb	Leaves	Used in constipation, cold and cough, fever, jaundice fatigue, weakness, indigestion, irregular menstruation, mouth ulcers, dysentery, leprosy and many others. It is also used in cardiac debility, asthma, epilepsy.
4.	Durba	<i>Cynodon dactylon</i> (L.) Pers.	Poaceae / Graminae	Small grass	Whole plant	Used in diuretic, anti-catarrhal, antipyretic, demulcent, leprosy, cholera, dropsy, diarrhoea, conjunctivitis.
5.	Mutha	<i>Cyperus rotundus</i> L.	Cyperaceae	Perennial Herb	Roots, Whole plant	Used in fever, different blood disease, dyspepsia, urinary disease. Plant juice used skin burning sensation, root used to fever with thirst.
6.	Lalkeru, Dudhia, Bara dudhe, Dugdika	<i>Euphorbia hirta</i> L.	Euphorbiaceae	Erect Herb	Leaves, Roots, Entire plant	Plant extract used in diarrhoea, bowel problems, colic, cold and cough. Latex used on nail corners infection, gonorrhoea, ringworms, sores etc.
7.	Pudina, Mentha	<i>Mentha piperita</i> L.	Lamiaceae (Labiatae)	Annual Herb	Leaves	Use to nausea, gastric stimulant, antiseptic, cold, cough, vomiting, sickness, local pains, , menstrual colic etc.
8.	Tulsi	<i>Ocimum sanctum</i> L.	Lamiaceae	Aromatic Herb	Leaves	Plan juice used to cure cold and cough, constipation, juice, cold fever, on ringworm, remove unwanted spot.
9.	Anantamul	<i>Hemidesmus indicus</i> (L.) R. Br.	Asclepiadaceae	Branched Shrub	Roots	Used kidney disorders, appetite, indigestion fever, diarrhoea, skin, piles, ulcers, stone kidney, leucorrhoea, syphilis.

Ethnomedicinal Uses

10.	Ayapan/Ayyapan /Aiapana	<i>Ayapana triplinervis</i> (M. Vahl.) R. King & H. Robinson	Asteraceae / Compositae	Perennial Herb	Leaves	Used to jaundice, intestine ulcer, haemostatic foul ulcers low blood pressure. Dried leaves used to cardiac stimulant.
11.	Basak	<i>Adhatoda zeylanica</i> Medic.	Acanthaceae	Perennial Shrub	Leaves	Used in catarrh, diarrhoea, dysentery. Leaves extract used in cold, cough and bronchitis. Flowers used in ophthalmia, bark used for remove acidity, and indigestion.
12.	Apang, Apamarg	<i>Achyranthes aspera</i> L.	Amaranthaceae	Perennial Herb	Entire Plant	Used in colic, piles, dropsy, gonorrhoea pneumonia etc.
13.	Aloe, Ghritkumari, Burn Plant	<i>Aloe vera</i> (L.) Burm.f.	Asphodelaceae	Shrub	Whole Plant	Used as skin treatment. It helps to heal wounds and burns. It reduces dental plaque, constipation, lowers blood sugar level.
14.	Arjun / Arjuna	<i>Terminalia arjuna</i> (Roxb.) Wight & Arn.	Combretaceae	Tree	Bark	Used in the treatment of wounds, hemorrhages, ulcers, heart diseases, & relieves hypertension
15.	Cinnamon, Daruchini	<i>Cinnamon sp</i>	Lauraceae	Tree	Bark	Cough, bronchitis, common cold problem.
16.	Indian bay leaf, tejpata	<i>Cinnamomum tamala</i> (Buch.-Ham.) T.Nees & C.H.Eberm.	Lauraceae	Tree	Leaves	Urinal problem, Blood urine
17.	Tentul	<i>Tamarindus indica</i> L.	Fabaceae	Tree	Bark	Reduce pain in digestive track, removes gases and effective in dysentery.
18.	Jasthi madhu	<i>Glycyrrhiza glabra</i> L.	Fabaceae	Perennial Herb	Root, Leaves	Cough, bronchitis, scalds of head.
19.	Turmeric	<i>Curcuma longa</i> L.	Zingiberaceae	Perennial Herb	Rhizomes	Urinal problem, used to relieve mild digestive problems, such as feelings of fullness and flatulence, skin diseases.
20.	Kalo Dhutra	<i>Datura innoxia</i> Mill.	Apocynaceae	Shrub	Whole Plant, Root, Leaves	Used in dog bite, epilepsy, dysentery.
21.	Akanda	<i>Calotropis sp.</i>	Apocynaceae	Shrub	Root, Leaves	Used in cough, asthma, dysentery. Cure leprosy, leucoderma, ulcer, tumour.
22.	Sita-Ashok	<i>Saraca asoka</i> (Roxb.) de Wilde LN.	Cesalpiniaceae	Tree	Leaf, seed & roots	It is best uterine tonic for strength of uterus
23.	Cluster Fig, Gular	<i>Ficus racemosa</i> L. Syb. F. glomerata Roxb. LN.	Moraceae	Tree	Root, bark, fruit & latex	Useful in measles, small pox and chicken pox leaves juice in jaundice
24.	Arandi, Castor Oil Plant	<i>Ricinus communis</i> L. LN.	Euphorbiaceae	Shrub	Leaves	Used for headache. Keeps away evil spirits, kaja prepared from fruits is applied in eyes.
25.	Naagbal	<i>Sida acuta</i> Burm.f. LN.	Malvaceae	Weed	Root, seed & leaves	Leaves in nervous & urinary disorders, in blood & bile disorders, in elephantiasis

26.	Bahera	<i>Terminalis bellerica</i> Roxb. LN.	Combretaceae	Tree	Bark	It is astringent tonic use, manage loss of appetite, thirst, bloating and flatulence
27.	Aswagandha	<i>Withania coagulans</i> Dunal LN.	Solanaceae	Shrub	Leaves, roots	Used in uterine disorders, it can boost brain function, lower blood sugar and cortisol levels, and help fight symptoms of anxiety and depression.
28.	Neem	<i>Azadirachta indica</i> LN.	Meliaceae	Tree	All parts	Used for heart and blood vessels, liver problems, skin diseases, appetite, diabetes.
29.	Bel, Wood Apple	<i>Aegle marmelos</i> Corr. ex Roxb. LN.	Rutaceae	Tree	Leaves, bark, fruit, seeds	It is beneficial in treating tuberculosis, hepatitis, ulcer and digestive problems, & in treating cholera.
30.	Punarnaba	<i>Boerhavia</i> sp .	Nyctaginaceae	Creeping	Root	Used in cough, alcoholism anaemia, jaundice, it simulates rheumatoid arthritis, intestinal colic, kidney disorders, skin diseases, insomnia, asthma.

CONCLUSION

Ethnomedicine or indigenous medicine has its immense value and medicinal significance. But traditional medicinal knowledge or traditional practices of treatment needed to explore and popularized for vast uses specially for poor and economically less developed population. These practice not only safe, affordable for folk people but also helpful for conservation and protect our biodiversity from our modern-day urbanization and industrialization.

ACKNOWLEDGEMENT

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Monoclonal Antibody in Cancer Therapy: Overview

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ABSTRACT

The use of monoclonal antibodies in recent years has achieved a considerable success in cancer therapy. Presently, along with surgery, radiation and chemotherapy, monoclonal antibody (mAb) based immunotherapy is regarded as an important mode of cancer therapy. During the last few decades, many monoclonal antibodies have been approved for cancer treatment. Though ADCC (antibody dependent cellular cytotoxicity) is regarded as the main mechanism of monoclonal antibody action, several modifications and improvements were made to the monoclonal antibodies to eradicate their side effects. A wide range of modifications and improvements have been to optimize the already prevailing systems. The multifaceted properties of mAbs and their simultaneous induction of long-lasting anti-tumor response as a therapeutic platform have given rise to newer strategies to fight cancer. The antigens and their receptors are overexpressed in cancer cells through various databases. Therefore, advanced studies using various techniques is the need of the hour for managing the disease. Our study focuses on categories, action mechanisms and clinical applications of the mAbs for cancer therapy. Cancer serology, resistance mechanism and tumor escape mechanism of mAbs have also been discussed here.

Keywords: *Monoclonal Antibody; Cancer Serology; Therapy; ADCC*

INTRODUCTION

Cancer treatment using monoclonal antibodies has reached a remarkable height of success in the past few years. Over the past two decades, antibody mediated therapy for treating the cancer has been considered as an important and most strategy strategies especially for the patients having hematological malignancies and solid tumors. Monoclonal antibodies are produced by fusing spleen cells from a rat which are immunized with a specific antigen and a mouse myeloma cell line. This is called Hybridoma technology.

However, trials with mouse mAbs had some drawbacks, they became more ineffective with repeated applications as the half-life of the antibody decreased during clinical trials. This happened due to the development of a human-anti-mouse antibody (HAMA) response in patients. In the late 1980s, "Fully – human" antibodies were derived from transgenic mice or yeast or phage systems. So, as a result of these innovations of antibody engineering, monoclonal antibodies proved effective in the treatment of cancer. In this paper we review the role of monoclonal antibodies in cancer therapy and its limitations.

LITERATURE REVIEW AND DISCUSSION

Monoclonal antibodies and their types:

Currently, various types of mAbs have been produced through antibody engineering. Although many of these antibodies share similar principles, they vary in targets and applications.

Murine mAbs:

Murine antibodies generally do not stimulate profound cytotoxicity but allergic reactions and anaphylactic shock may be induced by their repeated administration. Anti-CD3 mAb was initially approved for human treatment, but it was reported to be a great failure (Anasetti *et al.*, 1990). Murine mAbs which contain some foreign protein molecules, stimulates unfavourable responses in human patients during clinical use.

Chimeric mAbs:

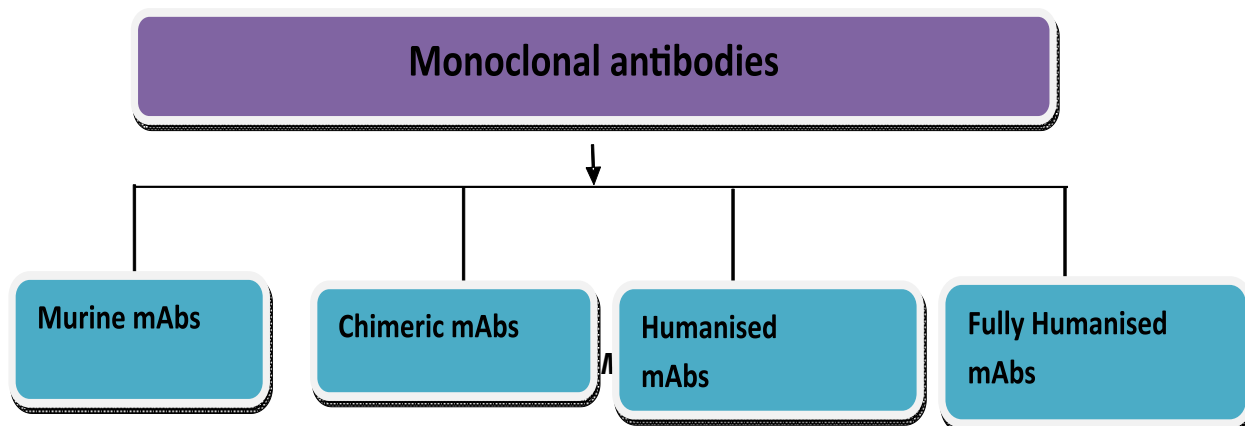
Special type antibodies from humans and non-humans (mice) combinations were the chimeric antibodies. They were produced by manipulation of mouse variable regions and human constant regions (Mendelsohn, 2001). 65% of human genetic components are used in these antibodies in order to minimize the unfavourable responses to foreign substances.

Humanized mAbs:

Humanized antibodies, are about 95% from human origin. Human mAbs have been recognized as natural drugs because of the safety in their usage (Marabelle & Gray, 2015). Daclizumab, omalizumab etc. are some examples of humanized antibodies which are approved by FDA.

Fully human mAb:

It is difficult to produce fully human mAb by the conventional Hybridoma techniques. However, eventually techniques were developed to produce human mAbs. The most well- established and most commonly used technique for the development of new human antibodies is the phage display technique., The first fully human mAb drug, Humira, was launched for the treatment of rheumatoid arthritis in the year 2003 (Lang, 2007).



Cancer serology:

In the past, with the aim of producing cancer specific antisera, many animal species were immunized with human cancers (Leach, Krummel & Allison, 1996). The discovery of the colon cancer marker-carcinoembryonic antigen (CEA) and other markers like α -fetoprotein had led to great progression in serological cancer investigation.

Tumor antigens as antibody targets:

The most important criteria of a tumor antigen to be the target antigen of monoclonal antibodies are that they must be accessible, expressed in high numbers and homogeneously, on the cancer cell surfaces. Also, the presence of the target antigen should be consistent and exclusive. Apart from the above-mentioned conditions, the Fc region should be easily available to immune effector cells and complement proteins. Some such tumour-associated antigens include CD20, CD30, CD33 and CD52. In some cases, mAbs target growth factors and growth factor receptors in patients. They include CEA2, ERBB2, ERBB, MET and insulin-like growth factor 1 receptor (Vermi *et al.*, 2018).

Clinical uses of monoclonal antibody:

Many types of mAb-derived treatments are being used clinically over the last few years. CD-20, found specifically in abundance on cancerous B-cells was the first target utilized in mAb associated therapy (de Haij *et al.*, 2010). A chimeric murine/human monoclonal IgG1 antibody called Rituximab could target

the CD20 B-cell surface antigen thereby mediating its lysis. Trastuzumab, a humanized IgG1 monoclonal antibody is used in treating breast cancer and gastric cancer. The mAbs like Bevacizumab (Printz, 2010), and Ranibzumab, are used to inhibit tumor-mediated angiogenesis. Other mAbs which are used in cancer immunotherapy are Pentuzumab, Ramucimumab, Olaratumab etc.

Mechanisms of Tumor escaping:

Tumor cells often escape the therapeutic effects of monoclonal antibodies. There are many reasons for such lack of tumor cell response to antibody treatment. Lack of therapeutic response in many cases may be due to mutation, heterogeneity in antigen or receptor size and affinity of antibody, permeability of blood vessels, low antibody-antigen ratio etc.

Combination Therapies of mAbs:

Success of monoclonal antibodies are seen when they are combined with chemotherapy or radiation. Few such approved combinations are combinations of Anti PD-1/PDL-1 with cetuximab In HNSCC patients (Giuliani & Marzola, 2014) and combination of Ipilimumab and anti-PD1 in metastatic melanoma patients (Li, 2021).

CONCLUSION

Inspite of being ineffective and intolerable in the case of first mAb which was approved for humans, today monoclonal antibody therapy has occupied an important position in the treatment of malignant cancers. The evolution of modified mAbs have improved their effectiveness and made the antibody-based drugs biosafe. Trials for combination therapies have demonstrated the encouraging pathways and need to be optimized for maximizing the clinical efficiency of mAb therapy. Further studies are necessary to be made on the aspects of mutations of tumor-associated target antigens and antibodies through research. Thus, future studies may help to establish mAbs as therapeutics for treating cancer.

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Review on Ruthenium (II) Anticancer Complexes: Challenges and Expectation

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ABSTRACT

“Once cancer happens it entirely changes the way of living for rest the life.” This statement is sufficient to show how dreadful cancer is. Cancer one of the huge killers in the universe from years. Several FDA approved anticancer drugs are organic molecules, while metal containing drugs are very less. Platinum based drug cisplatin, first metal based therapeutic design, launched a new era in the application of transition metal complexes for therapeutic design. In recent times Ruthenium based compounds have emerged as a promising anticancer agent that serve as an alternative to cisplatin and its derivatives, due to its versatile and unique biochemical properties. Over the past few decades ruthenium (III) complexes have successfully been used in clinical research and their action of mechanisms of anticancer have been reported in large volumes. Ruthenium (II) complexes have lured many attentions as anticancer candidate; however, only one or two complexes have been reported comprehensively. This review mainly focuses to show the new approach towards the field of metal based anticancer drugs. This review will focus on a short discussion on platinum therapies, a brief history of ruthenium anticancer compounds, followed by a study on ruthenium-DMSO complexes and, in particular, on NAMI-A. Many challenges are faced in this field from how to develop new ruthenium anticancer compound to how to select new active compound with clear anticancer activity.

Keywords: *Antimetastatic; Anticancer DMSO; Medicinal Inorganic Chemistry; Ruthenium*

INTRODUCTION

Cancer could be a major health burden within the world. Although many breakthroughs in biological targeted approaches have occurred, there's a necessity for the event and innovation of potential anticancer agents. In this virtue, metal complexes hold potential as novel anticancer agents for a large number of cancer types (Shi *et al.*, 2015; Benjamin Garbutcheon-Singh *et al.*, 2011; Li, Collins & Keene, 2015; Muhammad & Guo, 2014; Suntharalingam, Song & Lippard, 2014 & Liu *et al.*, 2016). This space is currently addressed with the utilization of platinum (II) coordination complexes, namely Cisplatin or cis-diamminedichloroplatinum (II) is the most generally known metal-based anticancer drug. Cisplatin is very effective against head, lung, ovarian, neck, and oesophageal cancers (Chu, 1994 & Cepeda *et al.*, 2007). Such platinum agents lack cellular selectivity and particularly liable to off-target effects, like peripheral neuropathy, baldness and myelotoxicity in patients (Sledge *et al.*, 1988; Arany & Safirstein, 2003; Florea & Büsselberg, 2011; Galluzzi *et al.*, 2012; Suntharalingam, Song & Lippard, 2014; Graf *et al.*, 2014). The resistance of tumours to platinum reduces the effectiveness of platinum-based or perhaps renders them ineffective, causing treatment failure (Dhar *et al.*, 2008a; Dhar *et al.*, 2008b; Fong *et al.*, 2016 & Cao *et al.*, 2016). Within the design of latest anticancer drugs, the interest in ruthenium (II/III) complexes has increased considerably (Abid, Shamsi, & Azam, 2016; Schmid *et al.*, 2007; Romero-Canelón, Salassa & Sadler, 2013; Liu *et al.*, 2010 & Ye *et al.*, 2014). Ruthenium complexes are tested against variety of neoplastic cell lines, and considered as the promising candidates for alternative drugs to cisplatin and its derivatives (Zhang & Lippard, 2003; Kostova, 2006; Smith & Therrien 2011; Liu *et al.*, 2016; Furrer & Süss-Fink, 2016; Levina, Mitra & Lay, 2010 & Hartinger *et al.*, 2008). This review will provide its reader with a sway of the recent development of ruthenium complexes as a promising anticancer agent (particularly NAMI-A).

REVIEW LITERATURE AND DISCUSSION

Platinum Therapies

From past few decades, within the field of metallo-anticancer therapies has been influenced by the dear metal Platinum. In the year 1965, at Michigan State University, Barnett Rosenberg during an experiment discovered the anticancer properties of Platinum. Rosenberg by employing a Platinum electrode applied an electrical field to a community of *E. coli*, which slow down their growth. An investigation was done, which concluded that the platinum electrode breaks all the way down to generate platinum (II) ion in place, which was inhibiting the cells from multiplying. These observations led to cis-diamminedichloroplatinum (II), commonly referred to as cisplatin. In 1978, Cisplatin was approved by FDA (American Food and medicines Administration) for the treatment of cancer. Since then, it becomes a widely used anticancer drug. Approximately, 70% of world's cancer patients receive this compound as a part of their treatment (Dorcier *et al.*, 2006).

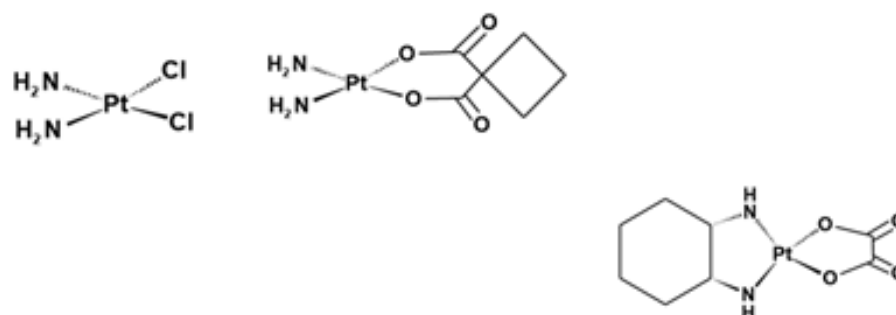


Figure 1: The Structure of Cisplatin[a], Carboplatin[b], and Oxiplatin[c] Takahara, Frederick & Lippard1996

Cisplatin

Cisplatin or cis-(PtCl₂(NH₃)₂) was a unique kind of anticancer drug, and its discovery given a lead to a group of scientist and researchers to perform tests on other valuable metal-based therapies. However, after endless clinical candidates and diverse research work, disappointingly in the world of metal containing anticancer drugs, there are only two more world-wide drug approval. Analogues of cisplatin namely carboplatin and Oxiplatin were approved by FDA in the year of 1993 and 2003 respectively.

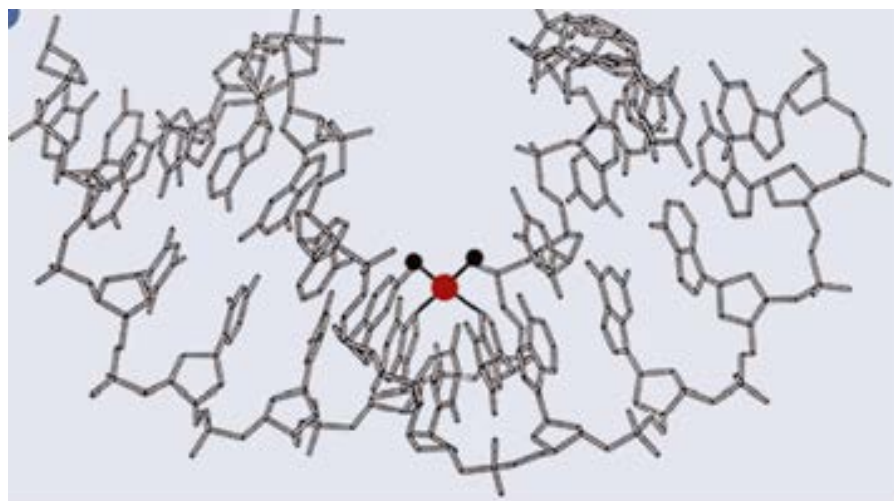


Figure 2: A Crystal Structure Showing Cisplatin (Red) Binding to DNA (Grey) (Takahara, Frederick & Lippard1996)

The mechanistic action of platinum-based anticancer drugs within the cell, a bis-aqua species is formed by the hydroxylation of the chloride or dicarboxylate ligands. The formation of bis-aqua species leads to the binding of two adjacent guanine bases of DNA irreversibly (Fig 2) (Takahara, Frederick & Lippard 1996).

From Platinum to Ruthenium

Platinum complexes by no means could be a perfect drug, though its chemotherapeutic success is undeniable. It's not effective against several kinds of cancer. The resistance in effectiveness of the drug is common. It also features a big selection of aftereffects, that are nerve damage, hair loss and nausea.

To avoid these side effects, scientists have developed compounds supported ruthenium and tested against neoplastic cell. Result shows that this ruthenium-based compounds tend to cause less damage to body compared to platinum drugs.

In pharmacological application properties of ruthenium are similar temperament. It can avail a variety of oxidation states (II, III and IV) and also it has relatively low energy barriers to interconversion between these oxidation states, allowing smooth conversion of oxidation states in the cell. Ruthenium complexes shows relatively low ligand exchange rates in water (Fig 3), thanks to flexibility in oxidation states.

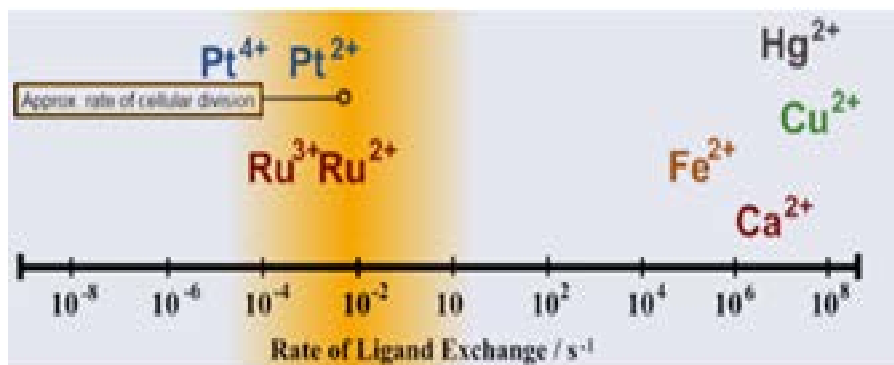


Figure 3: The Ligand Exchange Rates of Platinum Group Metals are Considerably

Ruthenium has the ability to make octahedral complexes, which allows the chemists to introduce more two ligands to take advantage. Whereas, platinum (II) complexes only adopt a square planar geometry. Ruthenium can bind to a spread of biomolecules, not only DNA. Ruthenium can form strong chemical bonds with many various elements of different chemical properties and electronegativity (Schluga *et al.*, 2006).

Less Toxicity of Ruthenium

Out of many assumptions, one assumption is that why platinum drugs are more toxic than ruthenium compounds are 'Activation by Reduction'. In keeping with this theory, ruthenium (II) complexes are less inert than ruthenium (III), which may be partially inherent due to its greater effective nuclear charge (Zeff). Chemically cancer cell needs a reduced environment than healthy cells, because their molecular oxygen concentration is low (due to unavailability from the blood supply). By considering the above two factors parallelly, ruthenium (III) (inert) causes a minimum damage to healthy cells, but when reduced to ruthenium (II) (active) causes heavy damage to the cancer cell lines (Vincent & Love, 2012). At last, ruthenium has the ability to copy iron in binding with several biological molecules, such as proteins (e.g., albumin and transferrin) which contribute to the overall low toxicity of ruthenium drugs.

Chemical Features of Ruthenium Compounds

Main chemical features of Ruthenium compounds are as follows

II, III and IV are the oxidation states that can be achieved by ruthenium. But only two oxidation states are chemically accessible for ruthenium compounds, which are relevant for biological activities. The

ruthenium (II) (diamagnetic, d6) and ruthenium (III) (paramagnetic, d5) are the oxidation states that are possible to access by ruthenium (Bergamo & Sava, 2007). With both the oxidation states ruthenium ion have six-coordinate with octahedral geometry. It shows good affinity towards sulphur and nitrogen ligands. As mentioned earlier that due to higher nuclear effective charge Ru (II) species is less inert than Ru (III) species. When a good π -acceptor ligand is present in air, Ru (II) species will remain unoxidized. Elaborately, ruthenium and platinum (II) complexes have more or less similar kinetics for ligand exchange.

In order to exert the anticancer activity, active ruthenium compounds have to coordinate with some biological target. Platinum drugs (prodrugs) should undergo an activation process which leads to the metabolites which are real active species. To understand the activity of some inert ruthenium (III) chloro-ammine compounds (such as *cis*-(RuCl₂(NH₃)₄)Cl and *fac*-(RuCl₃(NH₃)₃)), scientists concluded that reduction takes place followed by hydrolysis (activation by reduction hypothesis) (Clarke, Zhu, F & Frasca, 1999). This activation pathway is selective against solid tumours which are hypoxic, the reduction of ruthenium (III) to ruthenium (II) should be facilitated by insufficient circulation and having more reducing environments compared to normal tissues. Other source to tumour selectivity for Ru compounds is derived by their capability to bind with transferrin (serum protein). Compared to normal tissues, the tumour cell often express transferrin receptors excessively, due to their excessive iron uptake and a transferrin-mediated uptake have been evidenced for some ruthenium species (Clarke, 2002; Giaccone, 2000; Lippard *et al.*, 2003; Habtemariam *et al.*, 2005).

History

Historically, the chloro-ammine-ruthenium (III) compounds are primary ruthenium complexes to be studied for its anticancer activity. It is the ruthenium analogues of chloro-ammine-platinum compounds. In the year of 1980 Clarke along with his co-workers reported anticancer behaviour for *fac*-(RuCl₃(NH₃)₃) in mice models (Fig 4). *fac*-(RuCl₃(NH₃)₃) was not proceeded further, due to its negligible solubility which prevents it from adequate formulation as a drug (Clarke, Zhu & Frasca 1999).

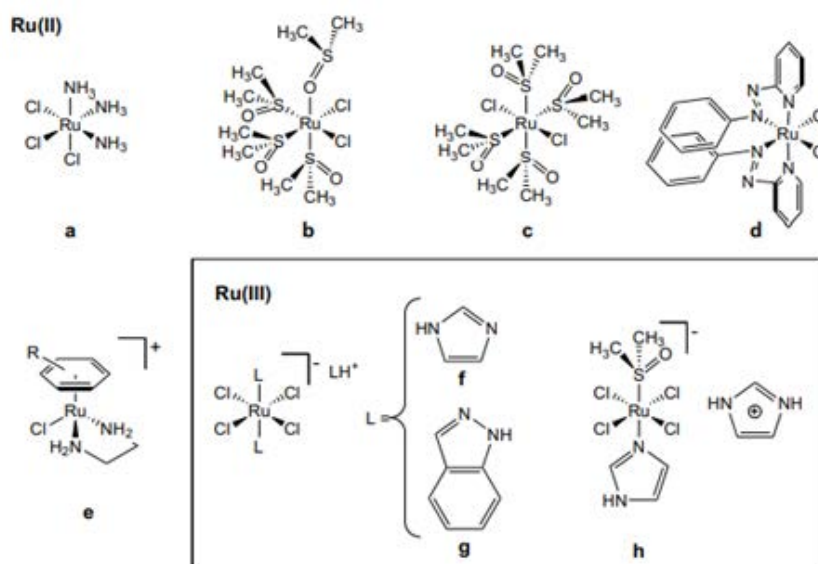


Figure 4 Structures of some ruthenium(II) and ruthenium(III)(inset) complexes that shows anticancer activity: [a] *fac* - [RuCl₃(NH₃)₃]; [b] *cis*-[RuCl₂(dmsO)₄]; [c] *trans*-[RuCl₂(dmsO)₄]; [d] *cis*-[RuCl₂(azpy)₂]; [e] organometallic compounds of general formula [(\eta₆-arene)Ru(en)Cl][PF₆]; [f] [ImH]trans-[RuCl₄(Im)₂] (ICR); [g] [IndH]trans-[RuCl₄(Ind)₂] (KP1019); [h] [ImH]trans-[RuCl₄(Im)(dmsO-S)] (NAMI-A) (Keppler, 1993; Sava, Alessio & Bergamo 1999; Alessio *et al.*, 2004; Groessel *et al.*, 2007)

4 years passed after the studies of fac- $(\text{RuCl}_3(\text{NH}_3)_3)$ was done, Mestroni and his team studied for the anticancer behaviour of a most commonly known ruthenium (II) complex, cis- $(\text{RuCl}_2(\text{dmsO})_4)$ (1, dmsO = dimethyl sulfoxide, Fig 4) (Mestroni *et al.*, 1994.). When compared to cisplatin, compound 1 is non-cytotoxic invitro and moreover, it possesses toxicity a minimum of three order of magnitude below that of platinum-based drug cisplatin. In mice bearing solid metastasing tumours, 1 showed activity against the first tumour and also in the metastases, when given at a most tolerated dose. Several studies show that the activity of ruthenium complex was similar to that of cisplatin but have an overall less host toxicity. The above results showed us a way to carry out scientific investigation of the anticancer activities of ruthenium-dmsO complexes (Mestroni *et al.*, 1994.). In the year of 1989 the trans isomer of ruthenium (II) complex $(\text{RuCl}_2(\text{dmsO})_4)$ (2, Fig 4) was more active than the former cis isomer 1 against lung carcinoma, a tumour with metastases. On molecular basis the cis isomer is less toxic than the trans isomer. Although trans isomer is more toxic, it is more practical in reducing the mass and amount of the ongoing metastases which is caused from the first tumour. Many experiments were carried out in which the tumour was removed surgically. Experimental studies showed us that when treated in mice the post-surgical survival time was more effective for compound 2 than platinum-based drug cisplatin. In other words, trans- $(\text{RuCl}_2(\text{dmsO})_4)$ have more selective activity against metastases, while in reducing the first tumour, cisplatin was more active (Mestroni *et al.*, 1994). Later on, other ruthenium-dmsO complexes also showed this feature.

The 80s showed a primary breakthrough in field of anticancer drug containing ruthenium: Keppler and his co-workers revealed (IndH)trans- (Ind) RuCl_4 (Ind) (KP1019, Ind = indazole) and (ImH)trans- (Im) RuCl_4 (Im) (ICR, Im=imidazole) (Fig 4) were two isostructural ruthenium (III) complexes that are active against variety of tumour model (Alessio *et al.*, 2004.). These results supported the essential premise of this field, i.e., that active complexes which does not have platinum centre, will be effective against platinum-resistant tumours, and further researches were proceeded. In the same year, while working on the preparation of the ruthenium (II) isomers 1 and 2, we isolated and characterized the dmsO analogue of Keppler's compounds, (dmsO)H(dmsO) trans- $(\text{RuCl}_4(\text{dmsO-S})_2)$. This compound, is not suitable for biological testing because of its very rapid hydrolysis at physiological pH, proved to be an excellent successor for ruthenium (III) compounds bearing both dmsO and heterocyclic N-ligands (L).

In early 90s scientists and researchers reported that (Na)trans- ((Im) $\text{RuCl}_4(\text{dmsO-S})$) (NAMI), which is structurally just like ICR having admso with S ligand that replaces an imidazole, is active against solid metastasizing tumours in mice (Keppler, 1993). Further, NAMI was replaced in pre-clinical trials by its imidazolium salt, (ImH)trans- (Im) $\text{RuCl}_4(\text{dmsO-S})$, called NAMI-A (Fig 4), which is an asset with the identical antimetastatic properties but is a more reproducible and stable solid and consequently is more fitted to further development in clinical phase. NAMI-A is capable of effectively restricting the development and growth of pulmonary metastases. Within the mouse which includes the non-small cell carcinoma in human tumour is xenografted in all mentioned experimental models of solid tumour were tested in vivo. Conversely, its activity towards the first tumour and cytotoxicity are negligible when compared to those of platinum-based anticancer drug. For instance, cisplatin is toxic against cellcultures at micro molar (μM) concentrations, while NAMI-A is void of toxicity up to milli molar (mM) concentrations.

After many preclinical tests, in the year of 1998 NAMI-A began clinical trials in European countries. Cancer Institute of Amsterdam became the first to begin clinical trials of NAMI-A. NAMI-A cleared this evaluation with great result. 24 patients were tested, all showed good tolerance over a good range of sub-toxic dose with no unexpected toxicity. Although there is no side effect but there form painful blisters, which was considered as to limit the dose of drug. 300 mg/m²/day was determined to be advised dose for further testing (Sava, Alessio & Bergamo, 1999.). Currently NAMI-A will begin phase 1-2 clinical trials.

In early 21st century, KP1019, developed by Keppler and his colleagues, entered into phase 1 clinical

trials (Alessio *et al.*, 2004). This compound is barely moderately toxic in cell culture tests, similar to NAMI-A. Presently, a pure new category of ruthenium (II) compounds was developed. Associates of Reedijk showed us that complexes with bidentate heterocyclic N-ligands like cis- $(\text{RuCl}_2(\text{azpy})_2)$ (azpy = 2-phenylazopyridine (Fig 4) possess significant toxicity (Alessio *et al.*, 2004.). Groups of Sadler (Sadler *et al.*, 1999; Sadler *et al.*, 2007.) and Dyson (Ang *et al.*, 2006 & Vock *et al.*, 2007.) developed Organometallic ruthenium (II)-arene compounds, which were found to possess in vivo activity. Particularly compounds with general formula $(\text{RuCl}(\eta^6\text{-arene})(\text{en}))(\text{PF}_6)$ (en = ethylenediamine) developed by the team of Sadler (Fig 4) showed faithful anti-cancer activity, both in vivo against animal tumour models and in vitro against human cancer cell lines.

NAMI-A

NAMI-A is a ruthenium anticancer complex that has entered clinical trials (Kostova, 2006; Lentz *et al.*, 2009). The trivial name NAMI is not considered as the abbreviation of “New Anticancer Metastasis Inhibitor”, but it bears a reasonable origin. It was formed as an acronym of the chemical formula of the complex: “NA” originated from the symbol of sodium and “MI” from the word imidazole. NAMI-A is the corresponding imidazolium salt. NAMI-A is nothing but are formed version of the prototype NAMI (Gou *et al.*, 2017) (Fig 5).

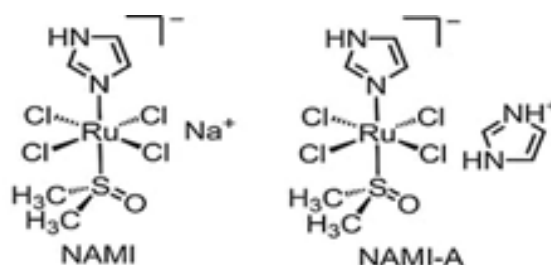


Figure 5: NAMI and NAMI-A

NAMI-A is primarily based for the use of the ruthenium metal. Ruthenium is not known to the living ecosystem; it has an ability to form strong complexes with numerous ligands (Gopal, Jayaraju & Kondapi, 1999). The ability to form complexes by NAMI-A is due to its partially filled 4d sub-shell. This complex forming ability makes it useful for a vast range of applications including electronics, photochemistry, catalysis, biosensor and anticancer drugs (Kostova, 2006 and Antonarakis & Emadi, 2010). Ruthenium has a greater resistance to hydrolysis, unlike traditional platinum complexes. It has also more selective action on tumours than platinum-based drugs.

The mechanistic action of NAMI-A (mostly unknown), is not related to direct tumour cell toxicity, hence it is responsible for decreased toxicity in host cell of this drug. NAMI-A in cell free medium is able to interact with DNA (similar to any d-block metal which is not fully inert). Nuclear DNA is not the obvious target of this drug. Thus, the working mechanism of action of this ruthenium (III) drug is readily distinguishable from platinum-based anticancer drug. Several features of NAMI-A are relevant for its metastasis's inhibition, including: (Keppler, 1993; Sava, Alessio & Bergamo, 1999; Alessio *et al.*, 2004; Groessl *et al.*, 2007).

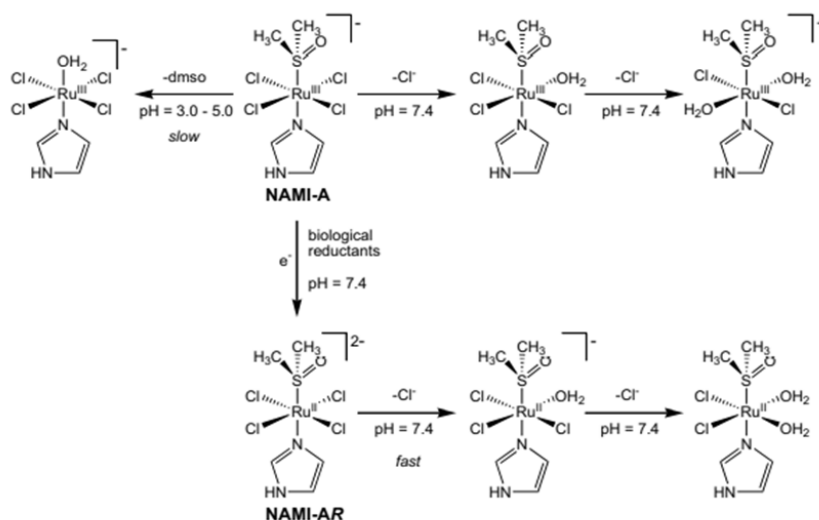
- Inhibition of matrix metallo proteinases and tumour cell invasion;
- Adhesion upregulation;
- Angiogenic activity downregulation;
- Caspase activation and inhibition of ERK1/2;
- The interaction with proteins and integrins is efficient.

Activation and Chemical Behaviour of NAMI-A

In the coordination sphere of NAMI-A, there a dmsol group is present. It controls the chemical behaviour

of NAMI-A. The dmsO group is involved in two step hydrolytic reactions whose nature and rate are strongly dependent on pH (Scheme 1) (Keppler, 1993; Sava, Alessio & Bergamo, 1999; Alessio *et al.*, 2004; Redemaker-Lakhai, *et al.*, 2004). The complex isn't inert, because it undergoes stepwise hydrolysis of two chlorides, under 37.0° C and 7.4 pH (phosphate buffer) within couple of minutes. the primary hydrolytic step is catalysed by ruthenium (II) species, of course the speed is influenced by addition of trace number of biological reductants, like antioxidant or cysteine. In between the partial dissociation of the dmsO, there lies the second hydrolytic step.

At any temperature NAMI-A is inert. In slightly acidic medium, dissociation of dmsO occurs slowly and the hydrolysis of chloride is suppressed (Alessio *et al.*, 1993 & Groessl *et al.*, 2007).



Scheme 1: Representation of the chemistry of NAMI-A under various conditions. (Keppler, 1993; Sava, Alessio & Bergamo, 1999; Alessio *et al.*, 2004)

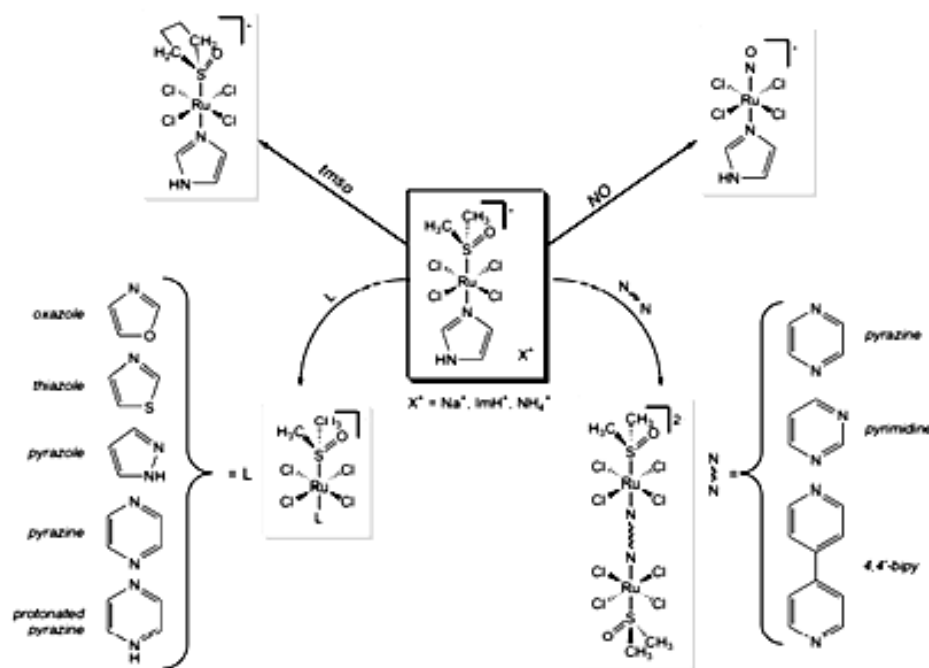
NAMI-A rapidly reduces to its corresponding dianion ruthenium (II) species trans- (RuCl₄(Im)(dmsO-S)²⁻, NAMI-AR, using catalytic amounts of commonly used biological electron donor or reducing agents (e.g., vitamin C, cysteine or glutathione) at physiological pH. Two chloride ligands of NAMI-AR undergo rapid stepwise hydrolysis (Scheme 1). Within the coordination sphere of NAMI-AR there is no loss of dmsO/imidazole or reoxidation by oxygen present in atmosphere is observed. Metabolites of NAMI-A that can bear the dmsO-S have reduction potentials almost like the parent compound and thus it is reduced easily (Ravera *et al.*, 2006).

Remarkably, ruthenium (III) and ruthenium (II) species with identical net charge, i.e., in mer-(RuCl₃(H₂O)(dmsO-S)(Im))-and NAMI-A the chloride dissociation has similar rates (Ravera *et al.*, 2006 & Schluga *et al.*, 2006).

To conclude, even NAMI-A is reduced to ruthenium (II) in vivo, the employment of biological reductants isn't needed for reduction. NAMI-A activation may occur easily through aquation, attributable to its relative lability at physiological pH. In other words, to elucidate the activity for NAMI-A the activation-by-reduction hypothesis is a concrete evidence. Contrastingly, anti-metastatic activity of NAMI-A is presumably associated with the presence of dmsO within the coordination sphere of its active metabolite(s).

Structure-Activity Relationships

As time pasts, to determine the structure activity relationship for NAMI-A, scientist have researched on every unit of the NAMI-A frame (Keppler, 1993; Sava, Alessio & Bergamo, 1999; Alessio *et al.*, 2004). A short conclusion on the results is given below (Scheme 2).



Scheme 2 Representation of the NAMI-A type compounds [Keppler *et al.*, 1993; Sava, Alessio & Bergamo, 1999; Alessio *et al.*, 2004; Alessio *et al.*, 1993; Groessl *et al.*, 2007; Ravera *et al.*, 2006; Schluga *et al.*, 2006; Hartmann *et al.*, 1998; Sava *et al.*, 2002.]

Many sulfoxides were tested, but scientist and researchers concluded that only tms (tetramethylenesulfoxide) is incredibly just like dms. This results in identical kind of ruthenium complexes. From biological and chemical point of view the (Na)trans-(RuCl₄(Im)(tms-S)) complex is almost similar to NAMI-A. A robust π-acceptor ligand NO may also successfully replace dms, which bind as NO⁺. It results in the reduction of ruthenium (III) to ruthenium (II). If we replace dms-S with NO⁺ in NAMI-A ends up in the formation of its derivative, diamagnetic complex ((Im)₂H) trans-(RuCl₄(Im)(NO)). It is slightly toxic to living cells *in vitro* but is barren of antimetastatic activity against *in vivo* models. (Alessio *et al.*, 1993; Groessl *et al.*, 2007 & Hartmann *et al.*, 1998).

N-ligand

This unit in NAMI-A framework may be effortlessly varied in an organised way (Scheme 2). In ruthenium (III) prototype ((dms)H(dms)) trans-(RuCl₄(dms-S)(dms-S)), under mild conditions one among the 2 trans S-bonded sulfoxides are often replaced by an outsized number of heterocyclic N-ligands (L), and also by NH₃ (ammonia), which leads to a series of NAMI-A types compounds with general formula (HL) trans-(RuCl₄(L)(dms-S)) (Alessio *et al.*, 2004). Researchers studied those compounds with increased lipophilicity and large aromatic ligands (L= quinoline and indazole), are less active than NAMI-A but are highly toxic, so they were not proceeded further. In slightly acidic medium (due to slower dissociation of dms) these compounds are more stable than NAMI-A. At physiological pH they act similarly to NAMI-A, which is useful for the purpose in view of the drug administration (Keppler, 1993). N-ligand of similar size and low basicity than imidazole (L=thiazole) having an *in vivo* effectiveness better than NAMI-A. If we use bridging ligands (L= pyrimidine, pyrazine or 4,4'-bipyridine) researchers developed binuclear compounds of formula (Na)₂. Each ruthenium centre contains a coordination environment same as NAMI-A type complex. The antimetastatic activity of these compound is reminiscent of that of NAMI-A (Keppler 1993; Sava, Alessio & Bergamo, 1999; Alessio *et al.*, 2004; Alessio *et al.*, 1993 & Groessl *et al.*, 2007).

Charge

In the time period of NAMI, chargeless ruthenium (III) complex mer-(RuCl₄(Im)(dmsO-O) (dmsO-S)), is derived from NAMI-A by replacing chloride ion with a dmsO with an O atom. It has an antimetastatic activity almost similar to that of NAMI-A. Thanks to poor solubility in water, this complex and similar neutral NAMI-A derivative were not proceeded further.

Chlorides

As mentioned earlier, chemical behaviour of NAMI-A and all NAMI-A type complexes showed a stepwise hydrolysis of minimum two chloride ions in physiological solution. After reduction of NAMI-A in vivo, dissociation of chloride is the main natural process that happens (Sava, Alessio & Bergamo, 1999). Thus, the strategy within the 80s in which platinum-based drugs from cisplatin to Oxiplatin to carboplatin may be worth to be pursued for active ruthenium-chloride-dmsO compounds. Significant differences in hydrolytic behaviour and its activity are predicted when the chloride in NAMI-A is replaced with chelating dicarboxylates. Despite, several efforts it is impossible to segregate any ruthenium (III) compound having both a chelating dicarboxylate and dmsO in the coordination sphere. Previously derived NAMI-A derivatives, either it failed to have dmsO any more or often it is ruthenium (II) species (Keppler, 1993; Sava, Alessio & Bergamo, 1999; Alessio *et al.*, 2004).

Oxidation State

It is discussed earlier, by using biological reductants NAMI-A is effectively reduced. Reduction of NAMI-A with water soluble vitamin gives NAMI-AR, in vial before administration. It is more practical than NAMI-A itself against metastasis growth. (Keppler, 1993; Sava, Alessio & Bergamo, 1999 & Alessio *et al.*, 2004).

Mechanism of Action

In recent times, the mechanistic action of NAMI-A results in a large number of concurrent mechanisms that will not involve nuclear DNA (Levina, Mitra & Lay, 2009). Sava *et al.* and his team members has done research work many years ago that NAMI-A will affect the tumour cells within the primary tumour (Sava *et al.*, 2003.) having metastatic ability. But it will sparsely affect the first tumour itself. The group of Sava (Gava *et al.*, 2006; Pelillo *et al.*, 2016; Casarsa *et al.*, 2004.) and Lay (Liu *et al.*, 2010.) investigated on different neoplastic cell lines that NAMI-A has the capability to significantly affect tumour cell with the ability of metastasis. It affects the tumour cell by interfering at sub-cytotoxic and physiological relevant ruthenium concentrations with tumour metastatic progression. More modern observations are there associated with this theorem. Remarkably, due to fast ligand exchange kinetics of NAMI-A, it is not internalised by cells. Compared to other ruthenium anticancer agents, there is a huge difference in mechanism, which are internalised by cells in large amounts. Studies performed by Aitken *et al.* that supported the difference in ruthenium uptake .

The binding of ruthenium to collagens of cell surface integrins and extracellular matrix, leads to the development of adhesion and also the invasiveness of cancer cell is reduced. The action of NAMI-A against fully grown metastases is perhaps more reasonably, because of its anti-angiogenic properties. It was confirmed within the chick chorioallantois and within rabbit eye cornea model (Vacca *et al.*, 2002; Morbidelli *et al.*, 2003).

CONCLUSION

The growth of NAMI-A is an impressive case study in the field of medicinal chemistry. Three decades of vigorous studies and research have produced huge amount of data on this compound, and this data helped NAMI-A to its introduction in clinical studies. There is success in the clinical trial, but it teaches us quite a few things.

Although NAMI-A has low stability and it undergoes facile chemical transformation, it is suitable for pharmacological testing and pharmacological testing. Like cisplatin and related platinum drugs, NAMI-A also behaves as a typical classical prodrug. Additionally, the toxicity of this compound is restricted and tolerable moreover it manifests a suitable solubility in biological fluids.

Investigated compound in clinical trials produce sparse evidence of systemic toxicity, which increases the chance of NAMI-A in clinical use. Though the anticancer activity is a limited once, used as a standalone factor, there is still many options to explore a bigger number of cancer models and it can be used in combination therapies.

Many scientific publications have been generated in this field of ruthenium drugs. However, a critical evaluation must be done, more and more attention should be given in separate ideas and concepts that are not been validated or myths from people who have found a solid experimental support or facts.

The mechanisms were not fully understood. Yet it seems like ruthenium complexes shows a multitargeted mode of action. There are still lots of space for new studies and there is a whole new understanding on taking advantages of latest technologies.

Finally, this review ends up by making it very useful for scientist and researchers for planning and preparation of higher ruthenium anticancer agents.

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Investigating the Pathomechanisms of Diabetic Retinopathy: The Cost of Diabetes

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ABSTRACT

Diabetic retinopathy is a major complication of diabetes that progressively damage the retinal blood vessels of people who have diabetes. It is the primary cause of blindness which has a significant effect on the world's health system. It is a disease which effects both type I and II diabetic patients at any stage of life. Diabetic Retinopathy is also one of the principal cause of blindness in adults in India. In some patients with Diabetic Retinopathy, blood vessels swell and leak fluid. In severe cases, new blood vessels are formed and abnormally grow on the surface of the retina. DR is the multi-factorial and a complex disease which effect the vasculature and photoreceptor functions of retina. Multiple biological, chemical, physiological and molecular alterations help to initiate and progress the diabetic retinopathy. A number of physiological pathways are changed in a pathological mode in the high sugar environment. These include blood retinal barrier dysfunction, capillary regeneration, glial cell dysfunctions and inflammation. This review aims to explore the pathomechanisms of diabetic retinopathy for easy understanding the disease.

Keywords: *Diabetic Retinopathy; PDR; NPDR; Retina*

INTRODUCTION

Diabetic retinopathy (DR) is a vascular disease mostly affects the structure and function of the microscopic vessels of retina which affects patients with diabetes mellitus (Figure 1). DR can be characterized into two clinical stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) (Sivakumar *et al.*, 2005). During early NPDR, the retina is damaged due to abnormal permeability and/or non-perfusion of capillaries which forms microaneurysms that is dilation of retinal blood vessels, absolute glaucoma and deposition of lipoprotein exudates. All the cellular components of retinal blood vessels are lost and results acellular capillaries. So, the main features of non-proliferative retinopathy are occlusion and abnormal dilation of retinal capillaries surrounding the zones where blood flow is absent and the zones surrounding the ischemia (Usman, 2018). Once the condition becomes more complex and severe, it transits first to pre-proliferative and lastly to proliferative retinopathy (Priya, Srinivasarao & Sharma, 2013).

LITERATURE REVIEW AND DISCUSSION

Neovascularization is the hallmark of pre-proliferative retinopathy. It leads to retinal ischemia and hypoxia. Leaking of fluid occurs from the abnormal capillary permeability; this is clinically known as macular oedema (MO) which impedes visual acuity (Ting *et al.*, 2002). Retinal capillaries are occluded which leads retinal ischemia. Ischemia stimulates the neovascularization by which new fragile and hemorrhagic blood vessels proliferate on the surface of retina. Blood is accumulated in the vitreous cavity from these hemorrhaging vessels and impairs the vision. Eventually it leads to retinal detachment and blindness. This visual impairment and associated complications have a negative impact on the quality of life and overall life expectancy of the patient.

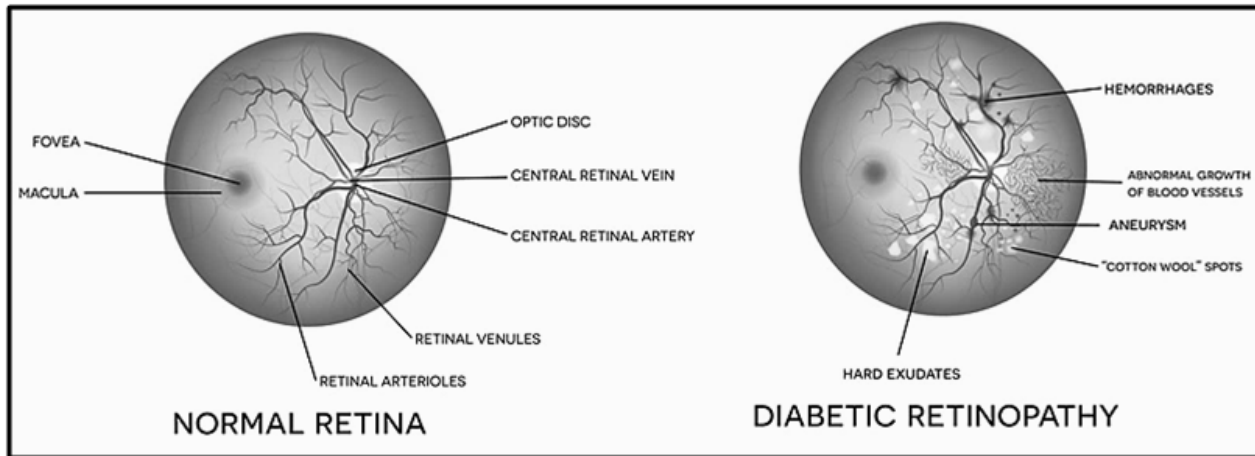


Figure 1: Normal vs diabetic eye. (source: www.eyef7.in/retina/diabetic-retinopathy/)

Statistics of DR

Diabetic retinopathy leads to major cause of vision loss due to microvascular complications. The main causes are increased urbanization, consumption of less-nutritious foods, sedentary lifestyles and obesity. Globally, 422 million adults were estimated with diabetes in 2014, compared to 108 million in 1980. In adult population, the global prevalence of diabetes has almost doubled since 1980. In the United States, the people between the ages of 20-64 is suffered from blindness due to diabetic retinopathy (Wilkinson *et al.*, 2003).

Over the past decade, the diabetes prevalence has increased in high-income countries. Presently, South East Asia and the Western Pacific account for more than half of adults with diabetes world-wide (Figure 2).

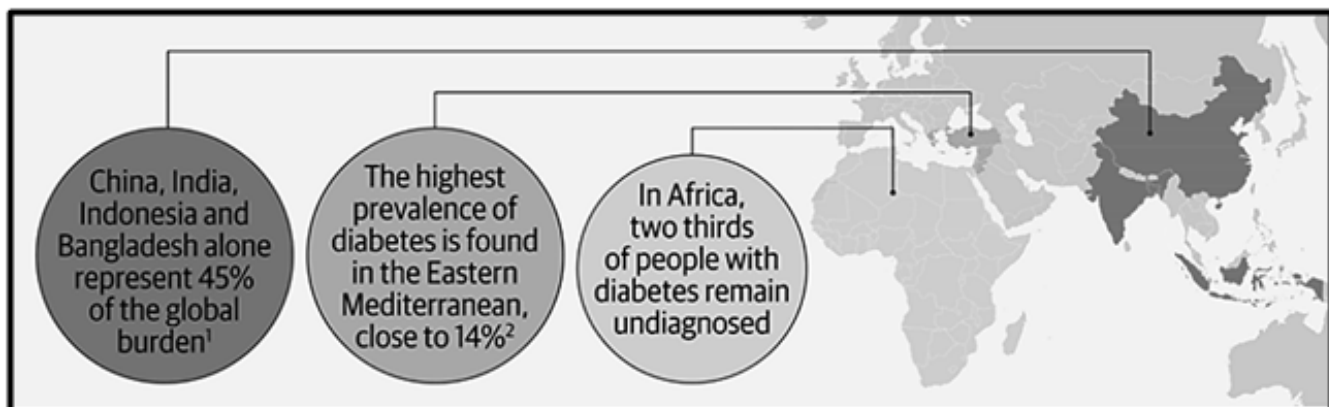


Figure 2: World-wide distribution of Diabetic. (source: atlas.iapb.org/vision-trends/diabetic-retinopathy)

The prevalence of diabetes mellitus is growing and complications are becoming major health issues which requires effective and active health interventions for disease control and treatment (Lang, 2007).

Epidemiology of DR

Vision Loss Expert Group of the Global Burden of Disease Study reported that in between 1990 and 2015, the crude prevalence of visual impairment and blindness due to diabetic retinopathy (DR) increased significantly in all age groups. In 2013, there were 382 million diabetic people and this number is estimated to rise to 592 million by 2035.

In an urban Chennai population, the age- and gender-adjusted prevalence rate of diabetes was 28.2% (95% confidence interval [CI], 27.0–29.3), and the prevalence of diabetic retinopathy in general population was 3.5% (95% CI, 3.49–3.54). Some factors are significantly associated with increased risk of diabetic retinopathy which includes gender (men at greater risk; odds ratio [OR], 1.41; 95% CI, 1.04–1.91); use of insulin (OR, 3.52; 95% CI, 2.05–6.02); duration of diabetes (>15 years; OR, 6.43; 95% CI, 3.18–12.90) and people with known diabetes mellitus (OR, 2.98; 95% CI, 1.72–5.17) (Raman *et al.*, 2008).

Current studies regarding the disease (International and National aspect)

Around 463 million adults (20-79 years) were diabetic in 2019 and by 2045 this will rise to 700 million (Saeedi *et al.*, 2019). The following Table 1 updates the recent international studies on DR.

Table 1: Descriptions of the international studies on DR.

SI No.	Topic	References with year
1	Prevalence of retinopathy in prediabetic patients.	Kirthi <i>et al.</i> , 2021
2	Vitreous metabolomics profiling.	Tomita <i>et al.</i> , 2021
3	Oxidative stress in DR.	Ortega <i>et al.</i> , 2021
4	Diabetic retinopathy screening.	Vujosevic <i>et al.</i> , 2020
5	micro RNA expression.	Zhou <i>et al.</i> , 2020
6	Role of antioxidants on diabetic retinopathy.	Garcia-Medina <i>et al.</i> , 2020

India, the contemplated diabetic capital of the world was predicted to hit 69.9 million of diabetic population by 2025. The main goal of this study was to evaluate prevalence as well as to explore the risk factors for developing DR among familiar diabetes. Figure 1.3 represents the prevalence of DR as reported by Gadkari. Prevalence of DR in respect of duration of diabetes, distribution of patients according to their age and prevalence of DR in patients with other end organ disease are also mentioned in the Table 2,3 and 4. Table 5 shows the recent studies on DR in India (Gadkari, Maskati & Nayak, 2016).

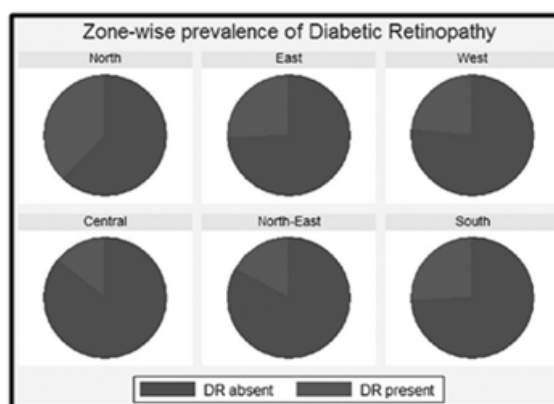


Figure 3: Zone-wise prevalence of diabetic retinopathy in India. (source: Gadkari, Maskati, & Nayak, 2016)

Table 2: Relation between duration of diabetes mellitus and prevalence of diabetic retinopathy. (source: Gadkari, Maskati, & Nayak, 2016)

Duration of DM	Prevalence of DR
<6 months	9.23
6 months-5 years	15.12
>5 years	35.12

DM: Diabetes mellitus, DR: Diabetic retinopathy

Table 3: Relation between age and the prevalence of diabetic retinopathy. (source: Gadkari, 2016) in the last sent manuscript

Age in years	Diabetic retinopathy			Prevalence (%)
	Present	Absent	Total	
0-20	2	59	61	3.28
21-40	57	458	515	11.07
41-60	581	2079	2660	21.84
61-80	448	1341	1789	25.04
>80	13	43	56	23.21

Table 4: Relation between age and the prevalence of diabetic retinopathy. (source: Gadkari, Maskati & Nayak, 2016)

Relation to other end-organ disease	Prevalence (%)
Renal	42.86
Cardiac	29.34
Stroke	31.82
Others	22.47
No complications	21.06
Multiple	48.72

Table 5: Descriptions of the studies on DR in India

SI No.	Topic	References with year
1.	Single injection of intravitreal dexamethasone and diabetic muscular edema.	Vergheese, Ranjan, & Manayath, 2021
2.	Detection of DR using intuitionistic fuzzy digital convex envelope segmentation algorithm.	Meenakshi <i>et al.</i> , 2021
3.	Correlation between markers of renal function and diabetic retinopathy in type 2 diabetes.	Rajalakshmi <i>et al.</i> , 2020
4.	Tackling diabetic retinopathy from the grassroots.	Sivaprasad, 2020

The survey conducted by Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, New Delhi during the year of 2015-2019 showed 8.0% prevalence of familiar diabetic cases and 3.8% redesigned diabetic cases. The survey also studied the prevalence of DR in different age groups and it was found to have 18.6% prevalence in the 60-69 years' age group, 18.3% in the age group of 70-79 years and 18.4% in above 80 age group, while 50-59 years' age group showing a lower prevalence of 14.3% (Figure 4).

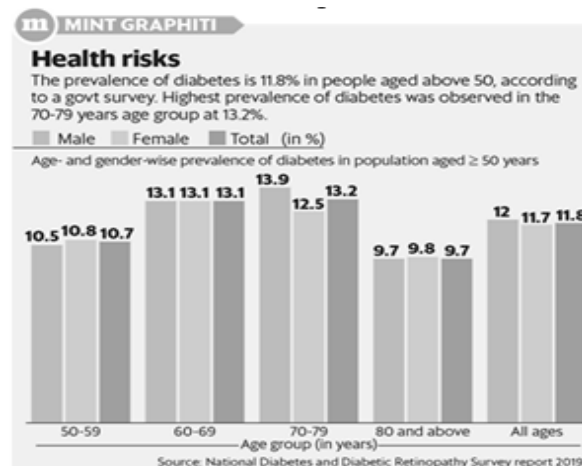


Figure 4: Government survey on diabetes in India. (source: <https://www.livemint.com/science/health/government-survey-found-11-8-prevalence-of-diabetes-in-india-11570702665713.html>)

Stages of diabetic retinopathy

Patients with type 1 or type 2 diabetes are at risk of developing diabetic retinopathy as well as diabetic macular edema (DME). Diabetic retinopathy may progress through four stages (Wilkinson *et al.*, 2003) (Figure 5).

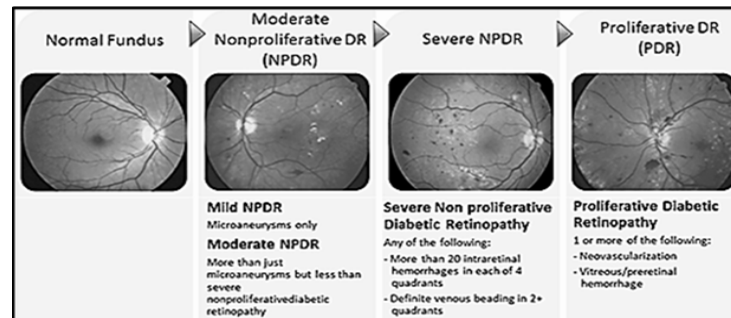


Figure 5: Stages of DR. (source: www.medscape.org/viewarticle/812590_2)

1. Mild non-proliferative retinopathy

At the early stages, balloon like swellings are found in the retinal blood vessels, these structures are called microaneurysms. These microaneurysms cause fluid leakage into the retina.

2. Moderate non-proliferative retinopathy

In this stage, the blood vessels of retina swells. It may also distort and cannot transport the blood. These conditions ultimately contribute to DME.

3. Severe non-proliferative retinopathy

In this stage, blood supply to retina is totally stopped because more blood vessels are blocked. Growth factors are secreted from these areas and induce the retina to form new blood vessels.

4. Proliferative diabetic retinopathy (PDR)

At advanced stage of diabetes, growth factors are secreted by the retina and help to proliferate the new blood vessels that grow on the inner surface of retina and then into the vitreous gel. But the new blood vessels are fragile, which continues them to leak and bleed. Scar tissues contract and cause retinal detachment from underlying tissue which leads to permanent vision loss.

Histopathological changes in retina

NPDR represents the early stage of DR. In this stage, two main observations are increased vascular permeability and capillary occlusion. Fundus photography can detect retinal pathologies including micro aneurysms, hemorrhages and hard exudates although the patient is asymptomatic. Neovascularization is a characteristic feature of PDR which is the most advanced stage of DR.

Blood-Retinal Barrier Dysfunction

During diabetic retinopathy, blood contents leak into the retinal neuropil because the inner blood-retinal barrier is compromised. Breakdown of the barrier results diabetic macular edema which ultimately leads to blindness (Chang *et al.*, 2006).

Basement membrane thickening of retinal endothelial cells

In human and experimental diabetes, the first histopathological change is vascular basement membrane thickening (Figure 6). It is found that thickening of basement results cell death and instability of blood vessels in the retina (Cai, 2002).

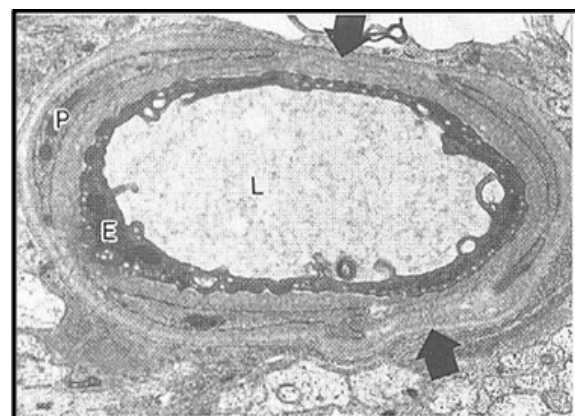


Figure 6: The thickened basement membrane (arrows). E=endothelial cell; P=pericyte; L=lumen (source: Anderson, 1995)

Capillary degeneration

Acellular capillary is a very common feature of DR. Smooth muscle cells of capillary are also lost and this capillary degeneration leads to ischemia in diabetic retinopathy which can be found in post-mortem retinas from long-term diabetic patients (Curtis *et al.*, 2009) (Figure 7).

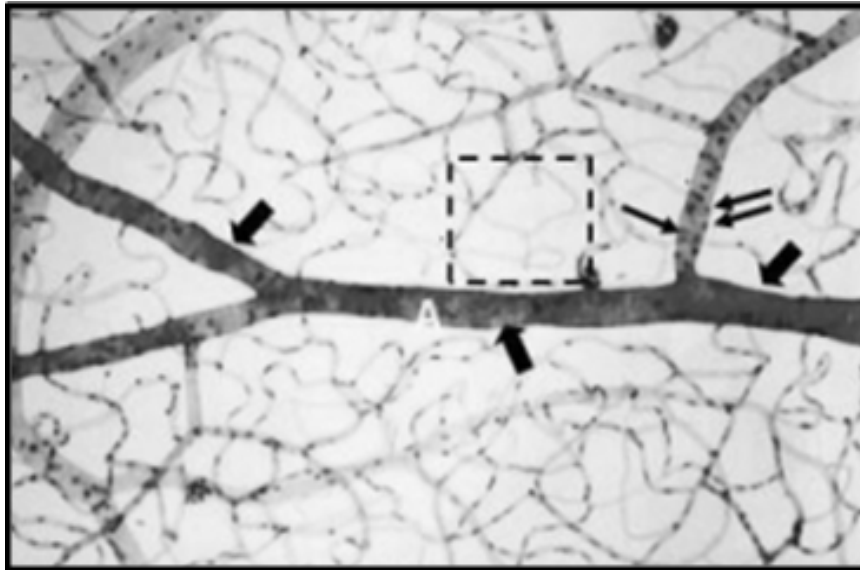


Figure 7: Absence of arterial smooth muscle cells (arrows) and capillary acellularity (dashed box). (Source: Curtis, Gardiner & Stitt, 2009)

Microaneurysms

Typical clinical feature of diabetic retinopathy is capillary microaneurysms. The capillary wall is outpouching like a balloon and associated with capillary degeneration (Kelaini, Cochrane, & Margariti, 2015) (Figure 8).

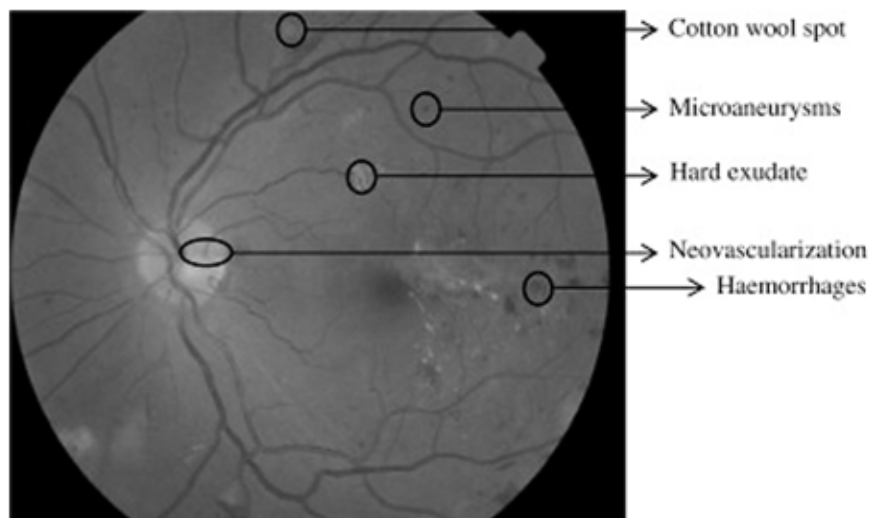


Figure 8: Micro aneurysms of diabetic eye. (Zaki *et al.*, 2013)

Risk factors

Generally, a person with diabetes mellitus may develop diabetic retinopathy. However, the main risk factors are (Figure 9),

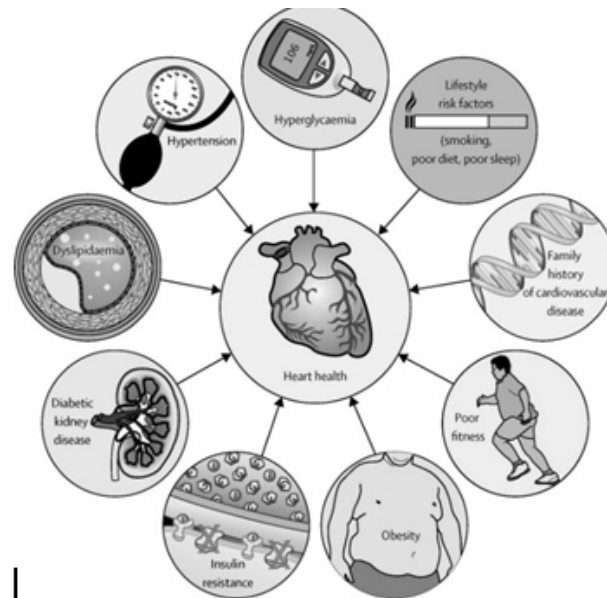


Figure 9: Risk factors with type 1 diabetes. (source: Bjornstad, Donaghue & Maahs, 2018)

Duration of diabetes: If the patient has diabetes for a long period.

Hypertension: Persons with high blood pressure and/or high cholesterol are also at greater risk (Schrier, 2000)

Poorly controlled blood sugar level: If sugar levels are poorly controlled and no medical steps have been taken to improve it, then DR can set in earlier. (Hardin *et al.*, 1956)

Hyperlipidaemia: Many studies have stated that lipid values have an effect on the initiation and progression of DR.

Smoking: Smoking is also a risk factor for development of DR.

Race: Hispanics and African Americans are at greater risk for developing diabetic retinopathy (Emanuele *et al.*, 2005).

Puberty and Pregnancy: Puberty and pregnancy exacerbate DR rapidly. Pregnant women face higher risk for diabetes as well as diabetic retinopathy. With a gestational diabetes, woman has a high risk of developing diabetes (Correa, Freitas & Marcon, 2003).

Body mass index: There are some positive correlation shown by some studies between the higher risk of DR and BMI and waist to hip ratio (WHR) (Seddon *et al.*, 2003).

Cataract surgery: Sometimes, intra-capsular extraction and extra-capsular cataract extraction surgery lead to DR progression (Xu *et al.*, 2011).

Inflammation: Chronic and/or low-grade inflammation play a role in the pathogenesis of DR (Joussen *et al.*, 2004). Various studies reported that the increased concentrations of chemokines like prostaglandins (PgE1, PgE2), stromal cell-derived factor (SDF-1 α), high-sensitivity C-reactive protein (hsCRP), intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1) and tumor necrosis factor alpha (TNF- α) are responsible for DR progression (Costagliola *et al.*, 2013).

Genetic factors: The onset of DR and its severity and rapidity is linked with several genetic factors including chromosome 1p, chromosomes 3 and 9, aldose reductase gene (ALR2), receptor for

advance glycation end products (RAGE) gene, transforming growth factor beta 1 (TGF-beta1) gene, vascular endothelial growth factor (VEGF) gene, endothelial nitric oxide synthase (eNOS) gene, vitamin D receptor and insulin-like growth factor 1 (IGF-I) gene.

Nephropathy: Kidney problem is more common in diabetic patients. It was predicted that nephropathy may be an early risk factor for type 1 diabetic patients. In 2010, this finding was published on the basis of the 15-year Beaver Dam Eye Study over 3,000 people. They concluded that nephropathy was a risk factor for new cases of severe retinopathy (Lindholm *et al.*, 2006).

Molecular and biochemical aspect of occurring DR

Diabetes induced complications can be elucidated by a number of cellular pathways and potential molecular mechanisms. It was found that all pathways end with increased oxidative stress, inflammation and vascular occlusion. These factors help to upregulate various factors that plays a pathogenic role in diabetic retinopathy (Figure 10 and 11).

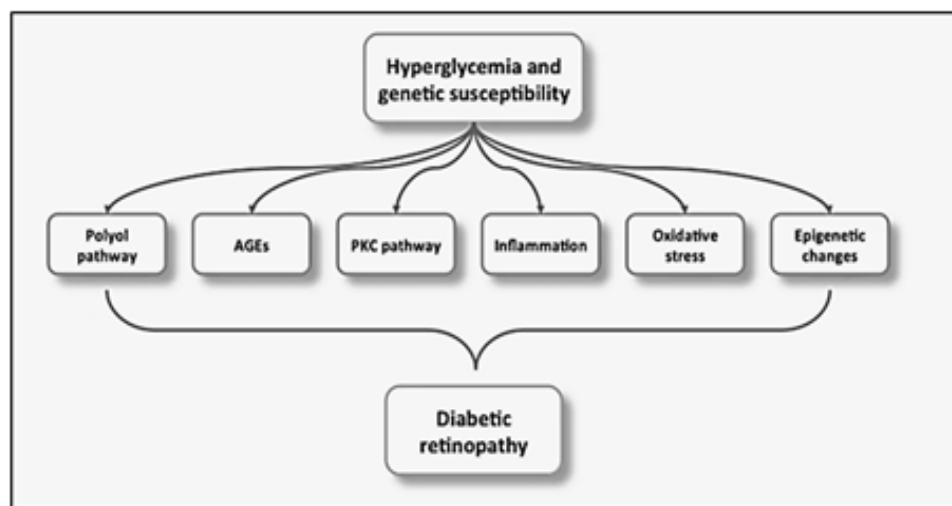


Figure 10: Altered molecular pathways lead to the development of DR. (source: Eshaq *et al.*, 2017).

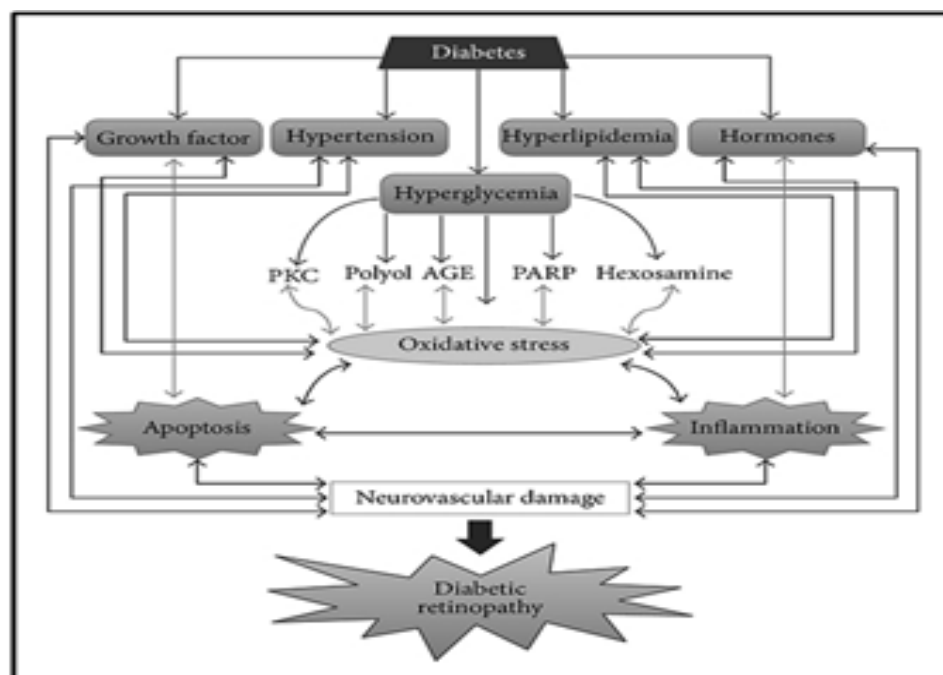


Figure 11: Hyperglycemia-induced diabetes related complications. (source: Safi *et al.*, 2014)

Increased Polyol Pathway Flux

In the polyol pathway, enzyme aldose reductase reduces glucose into sorbitol using NADPH as a cofactor. Sorbitol then converted into fructose by sorbitol dehydrogenase (Figure 12). Multiple damaging effects are found in retinal cells due to upregulation of sorbitol. Fructose produced by the polyol pathway is phosphorylated to fructose-3-phosphate. It breaks down then into 3-deoxyglucosone. Both are strong glycating agents and produce advanced glycation end products (AGEs) (Dagher *et al.*, 2004)

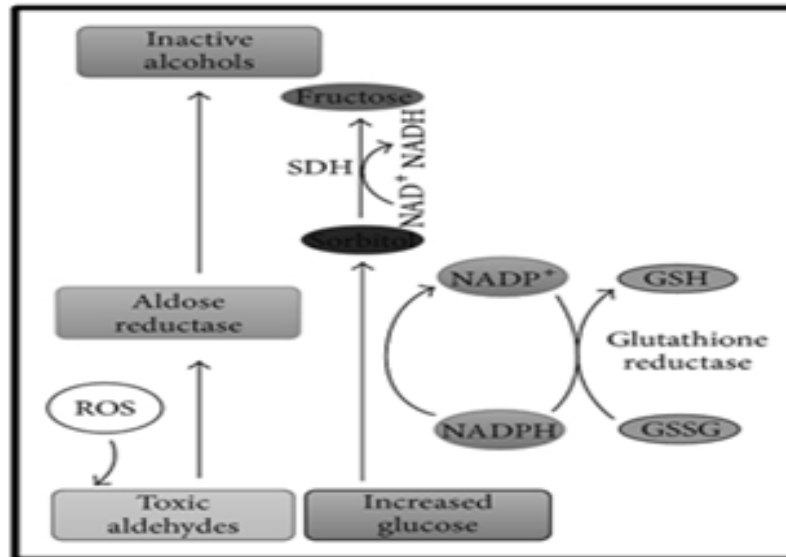


Figure 12: Aldose reductase and the polyol pathway. (source: Eshaq *et al.*, 2017)

Advanced Glycation products accumulation

Traditionally the chronic exposure of the retina to hyperglycaemia causes building up of advanced glycation end products (Figure 13) which have an important role in retinopathy (Zong, Ward & Stitt, 2011). Accumulation of AGEs gives rise to variety of vascular complications (Goldin *et al.*, 2006).

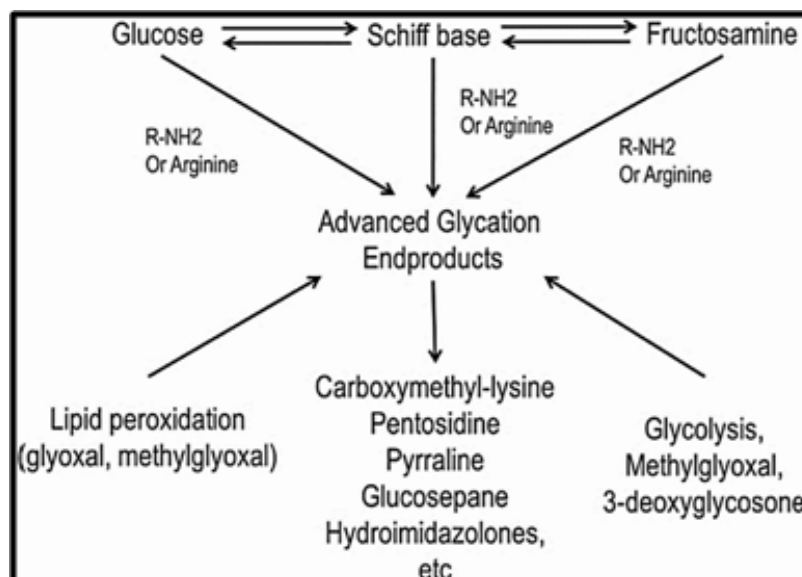


Figure 13: Formation of AGEs. (Gugliucci & Menini, 2014)

Hexosamine Pathway

It has found that diabetes causes increasement of hexosamine content in retinal tissues of humans as

well as in rats. Studies showed that insulin resistance is established due to the increased flux of glucose via the hexosamine pathway which result vascular complications and stimulation growth factor synthesis (Yang *et al.*, 1994) (Figure 14).

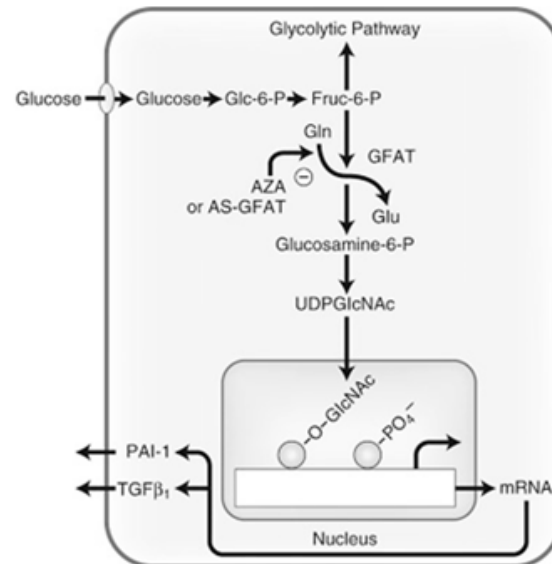


Figure 14: The hexosamine pathway. (source: Brownlee, 2016, Williams Textbook of Endocrinology, Thirteenth Edition)

Protein kinase C Pathway

It is reported that in diabetes hyperglycemia induced activation of protein kinase C cause many microvascular alterations in the retina of diabetic patients (Studer, Craven & DeRubertis, 1993) (Figure 15).

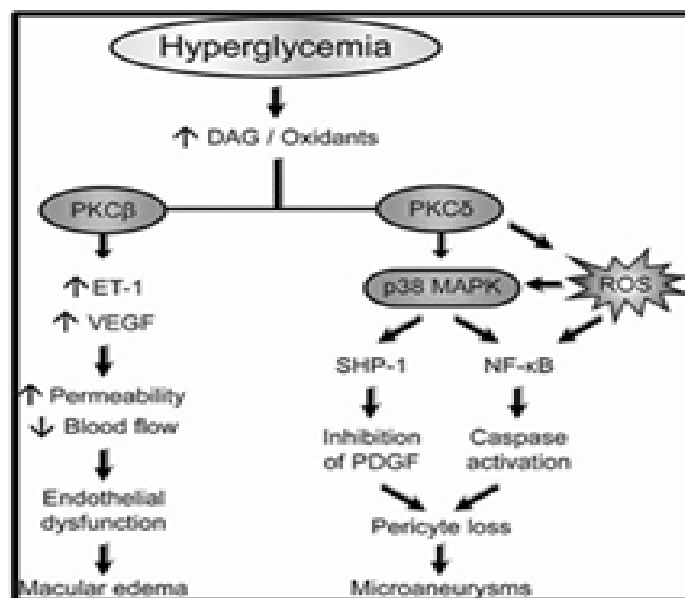


Figure 15: Target protein activation by PKC causing diabetic retinopathy. (source: Gerald & King, 2010)

Inflammation

Hyperglycemia creates a pro-inflammatory environment where help to overexpressed the inducible nitric oxide synthase (iNOS), leukotrienes, and cyclooxygenase -2 (COX-2). Hypoxia is the another

important factor in the diabetic retina which develop retinopathy because of capillary blockage or dropout. (Hammes *et al.*, 2003) (Figure 16).

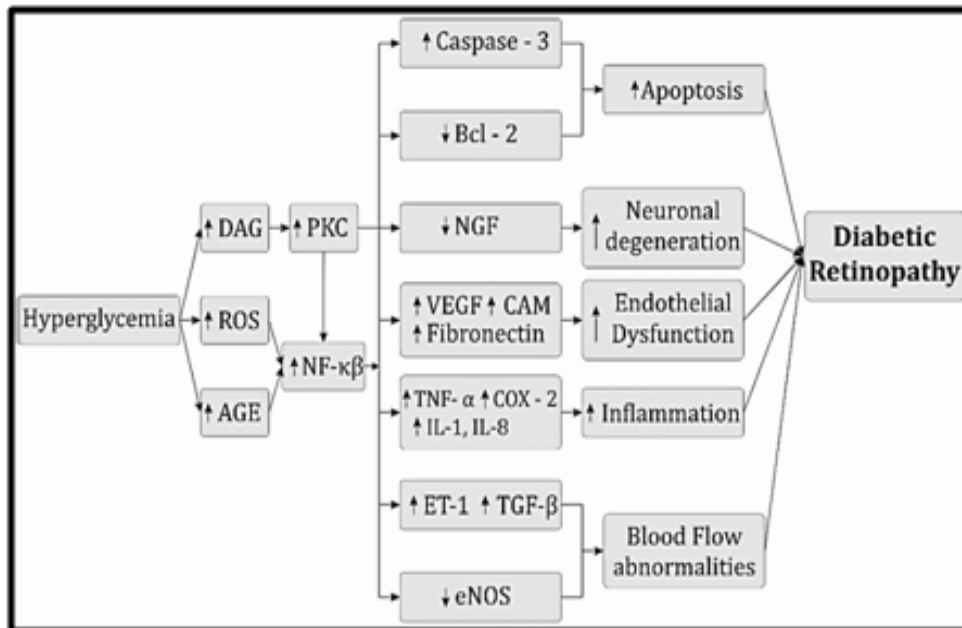


Figure 16: Role of inflammatory mediators in DR. (source: Suryavanshi & Kulkarni *et al.*, 2017)

Oxidative stress

In ordinary physiological conditions, reactive oxygen species (ROS) aids the body to kill the foreign materials that can leads to damage of the retinal cells. Hyperglycemia induces the formation of ROS, increased level of which activates many other pathways which help to initiate DR pathogenesis via up regulation of the poly-ADP-ribose polymerase (PARP) pathway as well as the down regulation of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) activity (Chaturvedi *et al.*, 1998).

Symptoms of diabetic retinopathy

Early stages of diabetic retinopathy usually are without of any symptoms. The disease often progresses unnoticed till it affects vision. "Floating" spots appears in the visual field due to bleeding from abnormal retinal blood vessels (Figure 17). Sometimes, the spots are clear on their own. But, sometimes, if left untreated, bleeding recurs which leads to permanent vision loss (Colucciello, 2004).

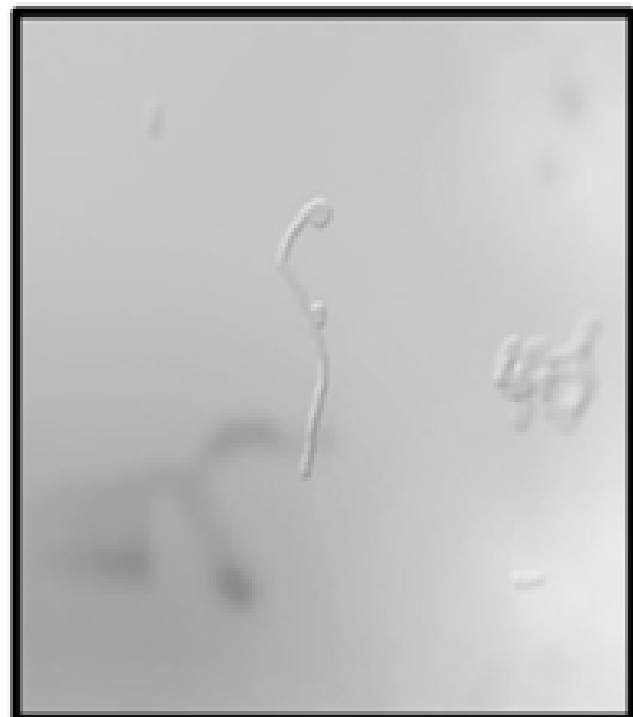


Figure 17: Eye floaters. (source: www.eyecareconcepts.com.au/eye-floaters-spots.html).

In case of diabetic macular edema (DME), it can cause blurred vision (Maheshwary *et al.*, 2010) (Figure 18). Blurriness is a common sign of retinopathy.



Figure 18: Blurred vision in DR. (source: www.justreverseddiabetes.com/diabetes-and-blurry-vision.html).

This disease can give a form of colour blindness. The reason for this is the same as the blurriness. The macula, the center part of the retina can become inflamed as well as the nerve fibres located there. It mainly causes blurry vision but also causing some people to have a hard time differentiating between colours. (Falkenstein, 2008).

Another symptom of this retinopathy is darkened areas within field of vision (Figure 19). This is most commonly reported in the center of visual field. However, it can be anywhere, and it can last for anywhere from a few minutes to days on end.

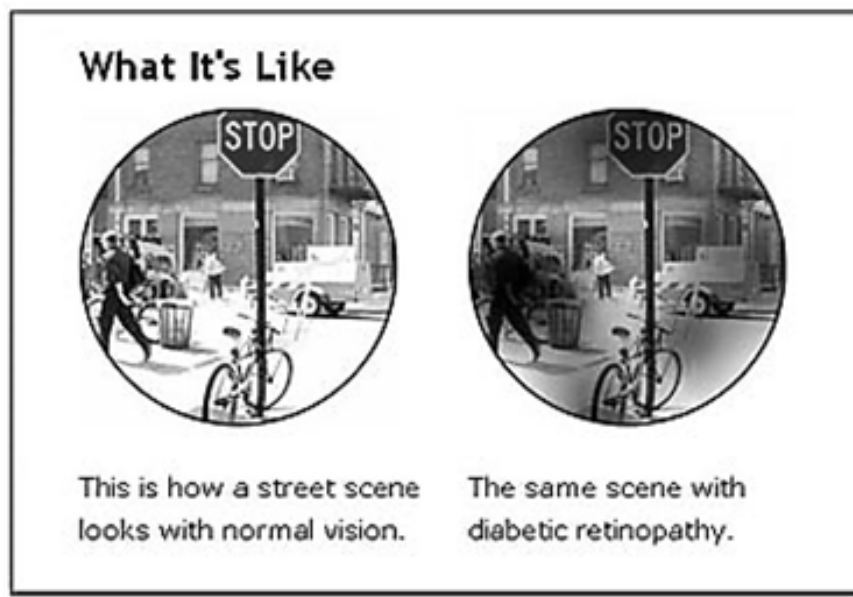


Figure 19: Darkened area at visual field. (source: li129-107.members.linode.com/about-low-vision-blindness/vision-disorders/diabetic-retinopathy/diabetic-retinopathy-overview/)

Diagnosis methods of DR

The present diagnosis methods for detection of DR are based on the following tests (Falkenstein *et al.*, 2008)

Detection of visual acuity

Trained ophthalmic technicians measured the best corrected visual acuity and calculated the minimum angle of resolution (MAR). In early treatment, Diabetic Retinopathy Study chart is used (Falkenstein *et al.*, 2008) (Figure 20).



Figure 20: Visual acuity test. (source: understandinyoureyeexam.weebly.com/visual-acuity-test.html) This test determines how well a patient can see shapes and letters at a specific distance.

Measurement of intraocular pressure

Ophthalmologists use the Tonometer for detection of intraocular pressure.

Examine the 'red reflex'

This is done with the ophthalmoscope held about 50 cm from the patient by examining the red reflection of light emerging from the eye. Both eyes are examined and compared.

Dilated funduscopy evaluation

To assess the severity of DR the stereoscopic fundus photograph is taken for detecting the retinal thickening, hard exudates etc. Presently the grading is done on the basis of having NPDR or PDR which is determined by the presence or absence of newly formed capillaries on the surface of the retina and into the vitreous.

Fluorescein angiogram

A fluorescein angiogram can be used to test the damaged or leaky blood vessel by using a fluorescent dye which is injected into an arm vein (Spaide, Lancins & Cooney, 2015)

Control measures of Diabetes

Risk factors of diabetic retinopathy includes hypertension, hyperglycemia, duration of diabetes etc. A study was coordinated by the diabetes control and complications trial (DCCT) in and according to their report, the acute treatment and improved glucose control slow down its progression compared to traditional treatment methods (Duh, Sun & Stitt, 2017).

Progression of diabetic retinopathy can be reduced by intensive glucose and blood pressure control

but it could be difficult to manage long-term management of these risk factors (Figure 21).



Figure 21: Target Blood Sugar Levels (adults)in diabetic patients. (source: <https://www.webmd.com/diabetes/guide/normal-blood-sugar-levels-chart-adults>)

Treatment

Both a doctor and an ophthalmologist are essential for the treatment of DR. Medical doctor helps to control blood sugar and can treat other diabetic related complications like kidney or heart malfunctions. Ophthalmologist uses vitrectomy (laser or a surgical procedure) which can treat directly diabetic retinopathy to stop additional vascular damages and try to preserve vision.

Photocoagulation

Photocoagulation is a laser treatment for diabetic retinopathy. It can create a burn in the target tissue and destroy the abnormal structures in the retina (Figure 22).

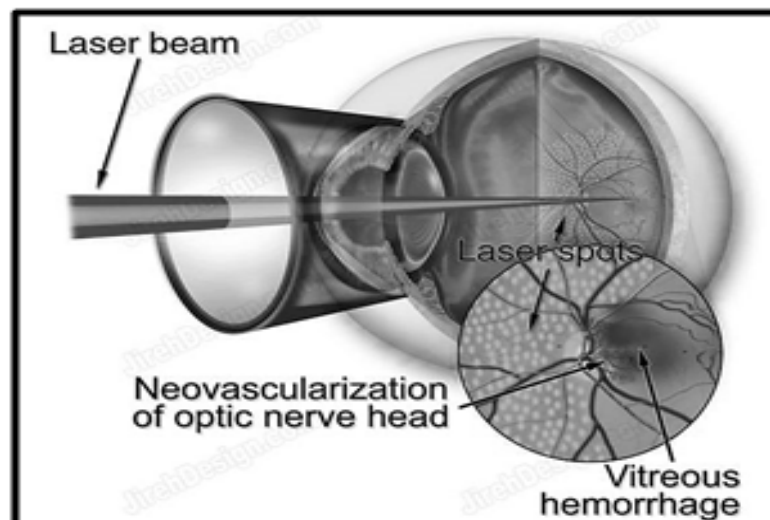


Figure 22: Photocoagulation method. (source: jirehdesign.com/stock-eye-illustrations/eye-surgery/retina-surgery-illustrations/argon-laser-diabetic-retinopathy-suvr0006/)

Vitrectomy

If patient has a hemorrhage may recommend vitrectomy surgery. During vitrectomy, ophthalmologist drains the fluid inside the eye, clear any lingering blood and remove scar tissue that causing poor vision. The vitreous is then restored with a substitute fluid (Figure 23).

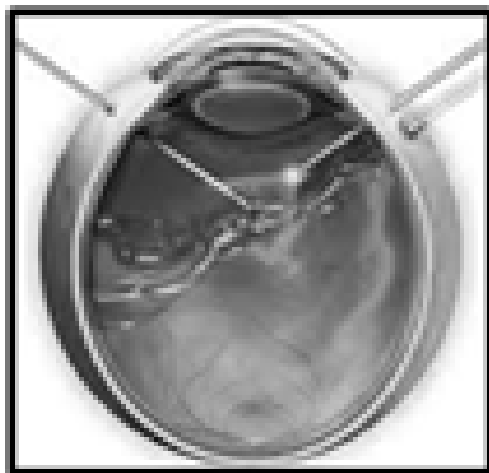


Figure 23: Procedure of vitrectomy. (source: svaretina.com/for-patients/common-disorders-treatments/vitrectomy-surgery/)

Anti-inflammatory treatment

In spitea vascular disease, many data suggest that inflammation is a potential risk factor for DR so the anti-inflammatory therapies may also veryeffective for treatment of DR. (Joussen *et al.*, 2002; Boyer *et al.*, 2014)

CONCLUSION

Diabetic retinopathy (DR) is the most common problem that causes progressively damage of retina of eye leading to vision impairment and blindness. From the 90s, occurrence of this complication has increased. In this review article, we interpret current statistics, different stages and medical aspects of DR. The review article illustrates the comparative study of prevalence, epidemiology current statics and current studies (National and International aspects) of disease which provides information on different stages of DR and histopathological changes of retina and elucidate symptoms, risk factors, different diagnosis methods of DR. It also manifests molecular and biochemical aspects of DR which includes multiple cellular pathways and potential molecular mechanisms. The review article unravels current image of DR and set forth different treatments of the disease which includes Photocoagulation, Vitrectomy, Anti-inflammatory treatment, VEGF inhibition, Erythropoietin inhibition and retinal microvascular surgery.

DR is one of the major causes of blindness in India and treatments can help. But this condition can't be cured completely so we need to improve awareness and provide proper care is indeed present. The aim of the review article is to reduce blindness due to diabetes by informing people and make them aware about the disease.

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Diversity of Poisonous Snakes in India

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ABSTRACT

Snakes are the integral part of the ecosystem. They are probably most misunderstood and universally disliked creature in world since time immemorial. Indian govt. implemented ban on trade of snake skins as they control rodents in agricultural fields. Some poisonous snake bite is may be fatal, but most of the bite is dry bite i.e. harmless to us. Among 285 species of snakes found in India, only four- spectacled cobra (*Najana naja*), Russell's viper (*Daboia russelii*), Common krait (*Bungarus caeruleus*), and saw-scaled viper (*Echis carinatus*), called Big Four are responsible for the majority of life-threatening bites. In India about one million people bitten by snakes annually and just one in twenty dies. Venomous snakebite can create various symptoms which includes swelling and restricted pain and might become extended up to convulsions, vomiting, and even paralysis. After snake bite the biting are should be clean up, with minimal body movement and immobilizing the affected part.

Keywords: Snake; Bite; Venom; Management

INTRODUCTION

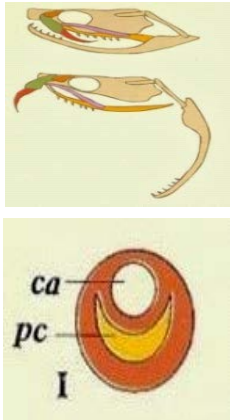
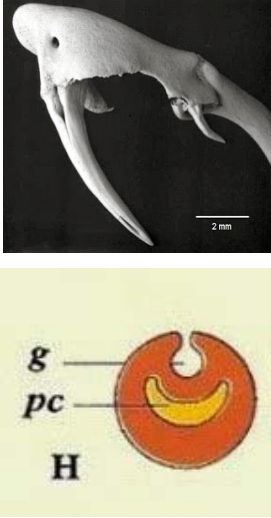
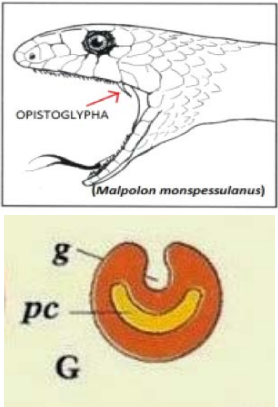
Snakes play significant role in ecosystem food chains. Snakes are found in different habitats from grasslands to wetlands, from agriculture fields to forests, and also around residential areas to deserts and sea. The snakes are predator of rodents, birds, amphibians and mammals. Most snake species are found in the dry zones. Maybe it's due to their capability to stay alive without food for a long time (Whitaker, 1978). Snakes are used to be predators of harmful insects and rodents in agriculture areas, but in India, due to lack of awareness hundreds of snakes are killed by the people. The venom machinery in the mouth of venomous snakes comprise a pair of fangs useful for the snakes to paralyze and kill the prey. Due to human fault of careless working in the agricultural areas without protection measures, the snake bite happens. Both venomous and nonvenomous snakes are killed without knowing the snake species. Across the globe people fear the snakes for insufficient knowledge resulting killing whenever and wherever they are seen (Kumar, 1991). All over the world, near about 3783 species of snakes are found, while in India among 518 species of reptiles 279 species are snakes within 28 families (Janani *et al.*, 2016). They constitute approximately 10 per cent of the total snake species found in the world and 80% of them are non-poisonous (Kale, Vairale & Ghait, 2019). The Venomous snakes comprise about 58 Species and there are only 4 species of snakes very dangerous to man, namely, Krait, Cobra, Saw-scaled viper and Russell's viper (Jadhav, Chavan & Trimukhe, 2018).

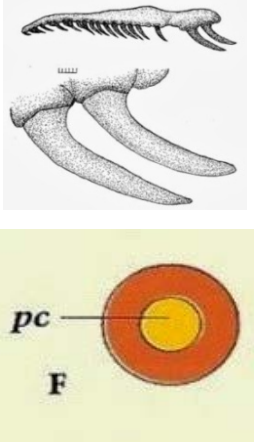
REVIEW LITERATURE AND DISCUSSION

Fang:

Snake fangs are dedicated, gracefully modified teeth. Some are like hypodermic needles; others are more like water slides (Table: 1). But all helping the same function: to inject venom into the snake's prey. Rarely, the fangs are used in defenses, but studies show that snakes striking in defense are far less prone to insert venom than when they're striking at a prey item.

Table 1: Types of fangs in snakes

TYPES OF FANG	STRUCTURE	DIAGRAM	FOUND IN
<p>Solenophis</p>	<p>Fangs are tubular and long attached to the maxillary bone. The maxilla is hinged so that the fangs can be fold back parallel to the jaw when the mouth is closed and erected when the snake is striking.</p>	 <p>ca= canal pc= pulp cavity I = solenophis</p>	<p>Vipers, rattlesnake</p>
<p>Proteroglyphous</p>	<p>Proteroglyphous fangs are in the front of the maxilla. Anterior surface bear groove.</p>	 <p>g= groove pc= pulp cavity H= proteroglyphous</p>	<p>Cobras, kraits, sea snake</p>
<p>Opisthoglyphous</p>	<p>They are found in the backside of the maxilla.</p>	 <p>g= groove pc= pulp cavity G= opisthoglyphous</p>	<p>Some colubrids, brown tree snake, green vine snake</p>

<p>Aglyphous</p>	<p>This is enlarged posterior maxillary teeth with lack of groove.</p>	 <p>pc= pulp cavity F= aglyphous</p>	<p>Common Indian Rock Python, Common Sand Boa</p>
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Venom apparatus:

The structure of venom apparatus in snakes varied, but some features remainsame. The venom releasemachinerycomprising set of fangs, venom ducts, a pair of accessory glands, and a pair of venom forming postorbital glands. These venom glands include three major cell types: conical mitochondria-rich cells, secretory cells, and basal cells which turn out venom (Figure 1).

Poison gland:

- In a venomous snake the poison gland at locaten one on either side of the apartment.
- Superior labial gland of the parotid gland modified into poison gland.
- Each venom gland is a satellite and provided with a narrow dark at its anterior end.

Venom duct:

- The duct passes forward along the side of the upper jaw and loops over itself just in front of the fang and opens either at the base of the fans or the base of the tunnel on the fangs.
- From the gland venom flows to the fang through the accessory gland.

Accessory gland:

- The accessory gland is the site of activation of venom components.

Fangs:

- There is one pair of fangs, located in various positions on the upper jaw.
- The fangs are used for bothvenom release during biting or spit venom.
- Maxillary teeth are transformed into enlarged and sharppoison fangs.
- There is the power of regeneration (when lost for some reason).

In viper, the maxilla is rotatable, which enables the fang to be erected during a bite or remain parallel to the jaw in a calm condition.

Inspite of various positions on upper jaw fangs are always located in maxilla. Moreover, in venomous elapids andcolubrid the venom fang is mounted in stable maxillary bone, and so that it is always remain erected. In viper the maxilla is rotatable, which enables the fang to be erected during a bite or remain parallel to jaw in relaxed condition. Superior snakes use venom for prey capture (Viperidae, colubrid,Actraspidae, Elapidae), are frequently referred to by the arrangement of their fangs may befront- or rear-fanged snakes. Majority of the medically important snakes are front-fanged (Viperidae and Elapidae) (Kumar, 2012).

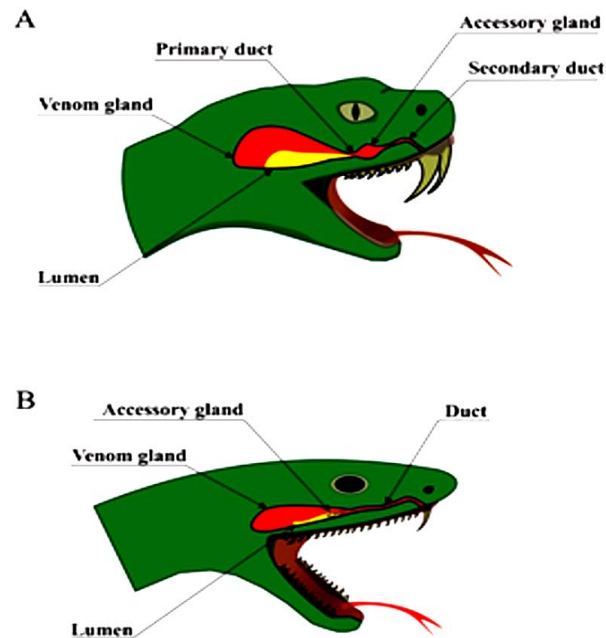


Figure 1: Snake Venom Delivery Apparatus. Schematic Anatomy of Snake Venom Delivery Systems (Jadhav, Chavan & Trimukhe, 2018)






Clinical features of snakebite:





Due to 'fear-factor' some people may develop strange signs and symptoms, even when no venom has been injected. Some develop numbness sensation in the extremities, ripple of their hands and feet, and vertigo. Shock may develop after the bite or assumed bite, with faintness and collapse with reflective slowing of the heart (Maheshwari & Mittal, 2004). Puzzling symptoms may appear with restlessness. With different age and size of snakebite victim the clinical appearance varies, the snake-species, the number and location of the bites, and the quantity and toxicity of the venom. Other factors of severity and outcome are listed in Table 1 (Janani *et al.*, 2016). The most common poisonous snakes in India are listed with their pictures, venom type and distribution in Table 3.

Table 2: Factors Effectingthe Severity in Snakebite

Factor	Effect on Outcome
Mass of the victim	Greater body mass has less amount of poison per kg of body weight.
Comorbidity	Older patients with comorbidity give up more easily to snake veom.
Part bitten	Patients bitten on the body, face, and straight into the blood have a bad predict.
Bite characteristics	Bite quantity, depth of bite, bite through clothing, or other guards, the quantity of poison inserted, condition of fangs, all involve the outcome.
Individual sensitivity	The compassion to venom varies from individual to individual.
Snake species	The effect of snake venom in victim varies from species to species.
Secondary infection	Presence or absence of microbes or pathogens in the mouth of the snake.
Treatment	Way of treatment using both first aid and antivenom dose.

Table 3: Commonpoisonous Snakes of India

NAME	PICTURE	FOUND IN	VENOM TYPE
Russell's viper (<i>Daboiarusselii</i>)		Almost all parts of India except certain parts of the western deserts and the freezing temperature of the Himalayas (Sulabh & Shivahre, 2017).	Its venom has mainly haemotoxic characteristic but the neurotoxin content of the venom is also very potent.
Common krait (<i>Bungaruscaeruleus</i>)		Agricultural fields, among short shrubs as well as in deep jungle and also around human habitation (Kularatne, 2002).	Neurotoxic venom
Banded Krait (<i>Bungarusfasciatus</i>)		They are found in the eastern part of India.	Neurotoxic venom
Sea kraits		Found in the Indian and the Pacific Ocean along the coast and coral reefs.	Neurotoxic venom, Myotoxic venom
Spectacled Cobra (<i>Najanaja</i>)		Found in most of the varied terrains of India. They usually prefer forest areas and dense jungles (Gan, 2002).	Neurotoxic venom (Huang & Kwan, 1996)

<p>Saw-scaled viper (<i>Echiscarinatus</i>)</p>		<p>Found in northern and southern India.</p>	<p>haemotoxic venom neurotoxic venom</p>
<p>King Cobra (<i>Ophiophagus hannah</i>)</p>		<p>Found in India all along the Western Ghats, the eastern coasts of Andhra Pradesh and Orissa, the northeastern jungles and tea gardens as well as the lower Foothills of Himalayas.</p>	<p>Neurotoxic venom, cytotoxic venom. (Kumar <i>et al.</i>, 1999).</p>
<p>Malabar pit viper (<i>Trimeresurus malabaricus</i>)</p>		<p>Found along the coastal areas of Western Ghats comprising mostly of Kerala and covers the majority of Maharashtra</p>	<p>Haemotoxic venom</p>
<p>Bamboo pit viper (<i>Trimeresurus gramineus</i>)</p>		<p>Found only in southern India, these snakes make perfect camouflage for the green shades of bamboo and other trees (Kale, Vairale & Ghait, 2019).</p>	<p>Haemotoxic venom</p>

CONCLUSION

Snake and the mildly venomous vine snake. Though many different kinds of poisonous snakes are found in India the snakes most commonly found to cause death. Polyvalent anti-venom containing anti-venom of all the big four poisonous snakes has been developed. However, it is not sufficiently potent to completely eradicate deaths caused due to the bite of any of the big four. Every species of snake has different constituents in its venom and require specific anti-venom preparation, to make anti-venom more efficient and potent. The anti-venom should be prepared specifically according to the species of the snake delivering the poison. This is also the reason for less potency of the polyvalent anti-venoms prepared against the big four snakes, which is used when the identification of the species to which the snake belongs is not possible. So, a much specific approach towards the development of anti-venoms exactly according to the type of snake would be a better alternative. General teaching and education of the common people about the identification of the common snakes will also help in resolving the matter more discretely.

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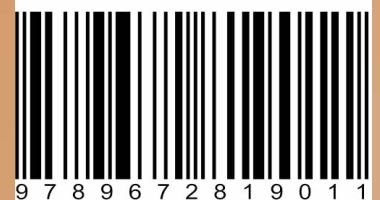
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