REVIEW ARTICLE

Therapeutic Efficacy of the Plant Bioactive Phytochemicals with Special Reference to Alkaloids, Terpenoids, Phenolics and Cardiac Glycosides

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Abstract

Medicinal plants constitute a vital part of the environment and ecosystem, playing an integral role in human health at a global level. These have a historical background of pharmacological relevance for curing various health-related issues. The therapeutic role of plants lies in the wealth of active principles that reside in their various parts. The plant-derived compounds or phytochemicals, including alkaloids, phenolics, terpenoids and cardiac glycosides, have constantly been evaluated and served as a vital source for drug discovery against numerous ailments such as diabetes, cancer, oxidative stress, respiratory problems, inflammation, cardiovascular diseases etc. Plant alkaloids are a group of organic bioactive compounds comprising nitrogen atoms in its chemical structure. Terpenoids comprise isoprenoid units, phenolics are aromatic metabolites with phenol hydroxyl groups, whereas cardiac glycosides are bioactive secondary phytochemicals that comprise aglycone linked to sugar molecules. These metabolites are biosynthesized through various biochemical mechanisms or pathways in the plant system. The enthusiasm towards bioactive compounds in therapeutics is because of its least side effects. India is a rich source of medicinal plants, making it one of the chief contributors in the pharmaceutical industry. The present review will discuss the therapeutic efficacy of phytochemicals with special reference to alkaloids, terpenoids, phenolic compounds and cardiac glycosides.

Keywords: Alkaloids, Cardiac glycosides, Phenolics, Terpenoids, Therapeutic.

Highlights

- The present review summarizes the therapeutic efficacy of phytochemicals derived from medicinal plants.
- The report provides an overview of the bioactive metabolites, alkaloids, terpenoids, phenolics and cardiac glycosides.
- The importance of this study on plant bioactive metabolites is firstly the pharmacological role that facilitates it to be one of the key sources for drug discovery against various ailments and secondly, it exhibits least side effects.
- In this review use of bioactive metabolites against health-related problems, including cancer, diabetes, respiratory, inflammation, cardiovascular etc., has been summarized.

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Introduction

Since ancient times all living organism rely for their survival on plants. Humans had always exploited plants for various purposes including its therapeutic use, simultaneously plants had also fulfilled majority of their requirement in various forms including medicinal for which it had always been in great demand at the global level. Medicinal plants are significant source of drug because of the existence of phytochemicals (Dhawale, 2013; Sharma *et al*., 2013; Okwu, 2004; Selvamohan *et al*., 2012). The term "Phytochemical" refers to an array of bioactive natural compounds exhibiting valuable pharmaceutical as well as nutritional properties (Kahkeshani *et al*., 2019). These compounds can be used either in standardized extract form or in purified form thereby offering a vital opportunity in novel drug identification. According to WHO, nearly eighty percent of the global population for their healthcare are dependent on traditional medicine (Schuster, 2001; Kunle, 2012). The therapeutic plants have been used not only for therapy but also for prevention and control of various diseases, including diabetes (Bahmani *et al*., 2014), lung diseases (Muhammad *et al*., 2021), antiplatelet agent (Ram *et al*., 2011), cardiovascular (Huang *et al*., 2021), neurological disorders (Akinmoladun *et al*., 2014; Ratheesh *et al*., 2017) etc.

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Plants system synthesizes secondary metabolites that facilitate them to exert an array of effects not only on the plants but also on other organisms (Teoh, 2015) upon interaction. However these usually occur in limited amount in comparison to primary metabolites through various pathways specifically through shikimate pathway, mevalonate pathway, methylerythritol phosphate pathway (MEP), tricarboxylic acid cycle (TCA) and also from primary metabolites (Teoh, 2015; Bruce and Felix, 2021). The primary metabolites are the vital precursors of secondary metabolites and are differentiated from the former in distribution, function and chemical structure (Jamwal *et al*., 2018). Phenolic are biosynthesized in the shikimate pathway

whereas terpene compounds are produced through mevalonic pathway (Jan *et al*., 2021). The metabolites containing nitrogen are biosynthesized in the pathway of tricarboxylic acid cycle (Jamwal *et al*., 2018; Jan *et al*., 2021). Quantitative estimation of these phytochemicals using standarised technique of Harborne (1973) was employed by various researchers at various times (Shoaib *et al.,* 2016; Gangaram *et al*., 2023).

For several years medicinal plants are considered as important therapeutic agents. In the present era the enthusiasm towards natural compounds had drawn a greater attention and is growing day by day. The reason is attributed to various factors including its neither or minor side effects and for this even at present majority of the plant's bioactive metabolites are implemented as an important source of medicines. The present review will mainly focus on the brief account on the therapeutic efficacy of the phytochemicals alkaloids, terpenoids, phenolics and cardiac glycosides derived from plants.

Plant bioactive metabolites

Alkaloids

Plants exhibits wide range of bioactive molecules including alkaloids. These are the large group of organic compounds exhibiting low molecular weight, occurring naturally and comprises nitrogen atom in their structure (Qurrat-Ul *et al*., 2016; Kurek, 2019). The term alkaloid refers to "alkali like" because of its basic nature and forms salts with acids (Kurek, 2019). These bioactive compound exhibits an array of pharmacological roles in various biological processes among living organisms (Facchini, 2001).

There are various classes of alkaloids such as indole alkaloids, isoquinolines alkaloids, quinolines, pyridines, pyrrolidines, tropanes, pyrrolizidines, steroids etc (Kaur and Arora, 2015; Kurek, 2019; Roy, 2017) that are ubiquitously distributed in the majority of plants species performing critical roles in an array of biological processes including defense processes in plants against pathogens and herbivores (Facchini, 2001). The medicinal value of alkaloids had also been unveiled by various researchers at various times (Mounir *et al*., 2021; Aryal *et al*., 2022). As for instance in *Panax ginseng* more than twelve alkaloids were reported (Liu *et al*., 2020). *Adhatoda vasica* contains alkaloids vasicine, vasicol, vasicinone, vasicinol, adhatodinine and deoxyvasicine (Claeson *et al*., 2000). Among these vasicine and vasicinone are reported to exhibit a potent bronchodialater, respiratory stimulant, antiallergic etc (Duraipandiyan *et al*., 2015; Liu *et al*., 2015). Alkaloids withanolides from root extract of *Withania somnifera* are reported to act against inflammation problems (Orru *et al*., 2023). The alkaloid content present in the bark of *Alstonia scholaris* is bitter, cardiotonic, antipyretic, anthelmintic, astringent, digestive, laxative and cardiotonic agent (Nadkarni, 1976).

The antidiabetic efficacy of plant alkaloids had also been reported as well as reviewed by various researchers (Bahmani *et al*., 2014; Rasouli *et al*., 2020). Alkaloids from stem and leaves of *Vinca rosea* are known to exhibit antidiabetic activity in diabetic rats induced by alloxan (Ahmed *et al*., 2010). Carbazole alkaloid present in stem, leaves, bark and root of *Murraya koenigii* (Jain *et al*., 2012) is reported as an active antidiabetic alkaloid (Muhammad *et al*., 2021). Besides being efficient as an antidiabetic agent several reviews had also focussed on active role of alkaloids as an anticancer agent (Dhyani *et al*., 2022; Twilley and Lall, 2018; Mounir *et al*., 2021). For instance an alkaloid palmatine (*Rutidea parviflora*) showed cytotoxic effect and apoptosis in ovarian cancerous cells (Johnson-Ajinwo *et al*., 2019). Metabolites obtained from *Colchicum luteum* and *Catharanthus roseus* also serve as an anticancerous agent (Dhyani *et al*., 2022).

Several bioactive compounds isolated from *Rauvolfia* species are reported to exhibit pharmacological value including the predominance of indole alkaloids such as reserpine, ajmalicine, ajmaline, rescinnamine, deserpidine and yohimbine (Boga *et al*., 2019). However the therapeutic activity of *Rauvolfia* is due to the presence of an array of alkaloids of which reserpine is vital. The total alkaloid content ranges from 1.7 to 3.0% in different sources and is usually concentrated in the bark of the roots (Krishnamurthi, 1981, Wealth of India, CSIR).

Reserpine from *Rauvolfia* species is effective as sedative or tranquilizing agent (Krishnamurthi, 1981). Ajmaline has been reported to stimulate respiration, intestinal movement and possesses antifibrillar activity (Krishnamurthi, 1981 Wealth of India, CSIR). It also in combination with antihypertensive agents is used for treatment of hypertension. Alkaloid rauwolfinine exhibits hypertension activity whereas rauwolscine causes hypotension (Krishnamurthi, 1981 Wealth of India, CSIR). The antimalarial property of several alkaloids had also been studied by researchers (Waako *et al*., 2007; Kuete and Efferth, 2010; Titanji *et al*., 2008; Ayuko *et al*., 2009; Uzor, 2020). Several alkaloids are also reported as antiplatelet agents. As per report of Lin and co-workers (2006) leonurine from *Leonurus sibircus* significantly inhibited platelet aggregation in rabbit. Huang and co-worker (2021) has also reported the therapeutic effect of rutaecarpine (Rut) the alkaloid obtained from *Evodia rutaecarpa* exhibiting potential and vital role as therapeutic agent for thromboembolic disorders (Huang *et al*., 2021). The therapeutic potential of the alkaloids is based on its mechanism of action, as for instance vinca alkaloids exhibits the antineoplastic property by inhibiting the formation of microspindle, its dissolution and arrest of metaphase in the cells (Dhyani *et al.,* 2022). Additionally alkaloids also plays a vital role against hyperglycemia by enhancing the consumption of glucose and synthesis of glycogen (Tang *et al*., 2017). The Table 1 depicts the summarised researches and reviews on the use of the phytochemicals.

Terpenoids

Plants are the vital source of secondary metabolite that is always used because of their therapeutic importance. Among these metabolites are the terpenoids that is most abundant in plants with around 25,000 kinds of compounds (Li *et al*., 2023). Terpenoids are secondary metabolites structurally composed of isoprenoid units (Paduch *et al*., 2007). These bioactive phytochemicals exhibit varied group of compounds occurring naturally and ubiquitously in plants. These are classified into mono-, di-, tri-, tetraterpenes and sesquiterpenes (Cox-Georgian *et al*., 2019).

Terpenoids plays critical role in plants including their growth and development, physiological processes and responses to environment (Yang *et al*., 2020). These are involved in defense reactions including abiotic and biotic stresses or as a signalling molecule in insect pollination (Singh and Sharma, 2015). In addition to plants, terpenoids had a wide range of medicinal

Table 1: Therapeutic efficacy of alkaloids

Alkaloids	*Therapeutic use*	*Reference*
Matrine and oxymatrine (*Sophora alopecuroides*)	Used for treating fever, antibacterial, gastrointestinal and heart disease and rheumatism	Wang *et al*., 2020
Indole alkaloids from *Alstonia scholaris*	Potent in few respiratory problems	Mitra *et al*., 2021.
Oxindole alkaloids (leaf and bark extracts from *Uncaria tomentosa*)	Exhibits anti-inflammatory activity in murine model of asthma.	Azevedo *et al*., 2018
16,17-Dihydro-17b-hydroxy from *Mitragyna parvifolia* is a isomitraphylline alkaloid	β-cells proliferation and descending apoptosis in pancreatic cell in diabetic treated rats induced by 16,17-Dihydro-17b-hydroxy	Shukla and Srinivasan, 2012
Rhynchophylline from *Uncaria rhynchophylla*	Exhibits neuroprotective role	Zeng *et al*., 2021
Canthinone (*Ailanthus altissima*)	Exhibited anti-inflammatory role in LPS-induced macrophages by downregulation of two pathways NF-κB and Akt.	Cho *et al*., 2018
Strychnos alkaloids from *Strychnos usambarensis*	Antiplasmodial and anticancerous activity	Frederich et al., 2002 Balde *et al*., 2010
Prenylindoles alkaloids (*Isolona cauliflora* and *Monodora angolensis*)	Effective as antifungal and antimalarial agent	Nkunya *et al*., 2004
Neferine (Nef) (*Nelumbo nucifera*)	Neferine targets cervical cancer cells, HeLa and SiHa by pro-oxidant anticancer mechanism; as apoptosis inducer in lung cancer.	Dasari *et al*., 2020; Paramasivan *et al*., 2014
Reserpine from *Rauwolifa serpentina*	Effective in hypertension	Lobay, 2015
Quinine, a cinchona alkaloid	Anti-malarial agent	Achan *et al*., 2011
Berberine, an isoquinoline alkaloid	Antimicrobial, bitter tonic, stomachic, potent in treating oriental sores.	Kulkarni and Dhir *et al.,* 2009
Colchicines from *Colchicum autumnale*	Treatment of gout and in acute gout attacks; binds to microtubular ends and inhibits polymerization of microtubule	Richette *et al*., 2017; Dhyani *et al*., 2022
Rhynchophylline; Isorhynchophylline from *Uncaria rhynchophylla*	Effective on central nervous and cardiovascular system.	Shi *et al*., 2003
1-carbomethoxy-β-carboline (*Portulaca oleracea*)	Effective in treating inflammatory diseases that involves MAPKs and NF-κB activation.	Kim *et al*., 2019

value in animal system and had been investigated, researched and reviewed for its importance at various times (Yang *et al*., 2020; Bergman *et al*., 2019) (Table 2). As per one review (Nuutinen, 2018) for centuries the therapeutic potential of terpenes in *Humulus lupulus* and *Cannabis sativa* are known for their efficacy not only in biomedicine but also in traditional medicine (Nuutinen, 2018). These compounds are applied in various pharmaceutical industries because of its activities like anticancer, anti-inflammatory (Del Prado-Audelo *et al*., 2021), antiviral, antibacterial, antimalarial, diabetes and cardiovascular diseases (Yang *et al*., 2020) etc. Terpenoids exhibits a range of actions because of their various targets in diverse cell components. For example terpenoids of plant origin inhibits the signalling of nuclear factor-kB, thereby exhibiting anti-inflammatory and anticancer potential (Salminena *et al.,* 2008). There are several reviews that focussed on the antineoplastic property of terpenoid compounds (Kamran *et al*., 2022; Huang *et al*., 2012; Klos and Chlubek, 2022). For instance terpenoids obtained from *Curcumae rhizoma* had been shown to be involved in broad spectrum with safe as well as high efficiency antitumour activities (Chen *et al*., 2021). As per the findings by Chen and co workers (2015) a Perillyl alcohol, a dietary monoterpene that were extracted from essential oils from aromatic plants like *Mentha piperita*, *Lavandula* exhibits an ability to inhibit progression of tumor in cell culture in addition to other therapeutic role in animal tumor models (Chen *et al*., 2015).

Phenolic compounds

Plants are rich source of phenolics with an array of distribution. These are the major group of bioactive phytochemicals exhibiting an array of therapeutic role that significantly facilitate in prevention of various types of health issues. Through pentose phosphate, shikimate and phenylpropanoid pathways phenolic compounds are biosynthesized (Randhir *et al*., 2004). These are aromatic metabolites that exhibit one or more than one phenol hydroxyl groups. Structurally they range from simple phenols to complex or highly polymerised phenolic compounds (Velderrain-Rodriguez *et al*., 2014). Phenolics naturally occurs in wide variety of plants including grains (Ciulu *et al*., 2018), legumes (Bodoira and Maestri, 2020), fruits and vegetables (Rana and Bhushan, 2016; Jaime *et al*., 2015; Diaz-de-Cerio *et al*., 2016). Simple phenols like catechol has been reported in the leaves of various species of *Gaultheria* of the family Ericaceae (Liu *et al.,* 2013). The seeds of *Macrotyloma uniflorum* also known as horse gram is the rich source of p-coumaric, a phenolic acid (Panda and Suresh, 2015). Whereas rosmarinic acid was found predominantely in *Salvia officinalis*, *Origanum* × *majoricum, P. longiflora,* and *Thymus vulgaris* (Zheng *et al*., 2001) etc.

Several researches and reviews had focused on the therapeutic role of phenolics in treating several health related issues in humans (Table 2). Phenolic acid had been recognised for its antioxidant (Martins *et al*., 2016), anticancerous or anticarcinogenic (Huang *et al*., 2010; Abotaleb *et al*., 2020),

Table 2: Therapeutic efficacy of plant derived Phenolics and Terpenoids compounds

Phenolics and terpenoids	*Therapeutic use*	*Reference*
Carvacrol (phenolic monoterpenes)occurs in essential oils of *Thymus vulgaris, Lepidium flavum, Citrus aurantium*, *Origanum vulgare* etc.	Antimicrobial, anticancer or antineoliptic, antioxidant, activities.	Wanda *et al*., 2023; Magi *et al* ., 2015; Sharifi -Rad *et al*., 2018
Protocatechuic acid (PCA) (*Hibiscus sabdariffa*)	Antioxidant and regulates hepatic damage in lipopolysaccharide-induced rats.	Lin *et al*., 2003
Carnosol and Carnosic acid *(Rosmarinus officinalis)*	Antiangiogenic properties	Lopez-Jimenez *et al*., 2013
Caffeic acid	Antidiabetic property C57BL/KsJ-db/db mice by regulating diabetes (type 2)	Jung *et al*., 2006
Vanillin (in several vanilla beans)	Effective in neuroprotection	Iannuzzi *et al*., 2023
Gallic acid	Antioxidant, anti-inflammatory, antineoplastic properties and effective against disorders such as neuropsychological, gastrointestinal, cardiovascular and metabolic disorders	Kahkeshani *et al*., 2019
Gallic acid in *Emblica officinalis*	Gallic acid mediates antidiabetic activity by delineating the upregulation of pAkt, PPAR-γ and Glut4, hence providing a efficient potential against diabetes and related disorders	Variya, *et al*., 2020
Oleanolic acid is a triterpenoids	Anti-inflammatory role	Fernandez-Aparicio *et al*., 2021
Oleanolic acid	Antitumorous potential in hepatocellular carcinoma in *in vitro* and *in vivo* models	Wang *et al*., 2013
Oleanolic acid	Enhances increased secretion of insulin	Teodoro *et al.,* 2008
Oleanolic acid	Oleanolic acid is effective in improving resistance against hepatic insulin through antioxidant, hypolipidemic and anti-inflammatory effect	Wang *et al*., 2013
Oleanolic acid	Antioxidant activities in *in vitro* models	Wang *et al*., 2010
Nomilin (triterpenoid) and Glycyrrhizic acid	Immunomodulatory role in Balb/c mice	Raphael and Kuttan, 2003
Ursolic acid (Pentacyclic terpenoid)	Anti-Inflammatory activities and immunomodulatory role in Balb/c mice	Dharambir *et al*., 2016; Raphael and Kuttan, 2003
Geraniol (isoprenoid monoterpene)	Anti-inflammatory, cardioprotective, antitumor, antioxidative, hepatoprotective, antimicrobial, and neuroprotective	Lei *et al*., 2019
limonene (monoterpene)	Serve as hepatoprotective agent in rat model in response to chronic immobilization	Amini *et al*., 2020

Table 3: Therapeutic efficacy of plant derived Cardiac Glycosides

Cardiac Glycosides	*Therapeutic use*	*Reference*
Oleandrin from *Nerium oleander* in Anvirzel™	Candidate as anti-HIV therapeutic.	Singh *et al*., 2013
Cerberin from *Cerbera odollam* and *C. manghas* (Bintaro)	Seeds of the *Cerbera* exhibits anticancer properties because of its potential in apoptosis	Saxena *et al*., 2022
Oleandrin (*N. oleander*)	antitumor promoting agent in an in vivo animal model by inhibiting markers of TPA-induced tumor promotion	Afaq *et al*., 2004
Oleandrin (*N. oleander*)	Exhibits antiviral activities and acute respiratory syndrome of SARS-CoV-2	Plante *et al* 2020
Digitoxin (*Digitalis purpurea*)	Potential anticancer agent	Pongrakhananon, 2013
Ouabain (*Stropanthus gratus*)	Potential anticancerous agent	Du *et al*., 2021

anti-inflammatory (Boo, 2019) gastroprotective (Panda and Suresh, 2015) and antimicrobial (Karunakaran *et al*., 2018) roles. The antioxidant potentiality of plant phenolics depends on its reaction with an array of free radicals (Zeb, 2020). Furthermore this bioactive compound interacts with a range of molecular targets vital to signalling processes in cells (Soobrattee *et al*., 2005). In addition to these the phytochemical plays a vital role in diabetes (Deka *et al*., 2022). The role of naturally occurring phenolics in neuroprotection and its mechanism of neuroprotective actions were reviewed by Kim (2010). Additionally phenolic acid are also actively potent in gastroprotection. The influence of phenolic acids extracted from *Macrotyloma uniflorum* on rat model

with gastric ulcer was studied by Panda and co-worker (2015). Furthermore Yoo and co-worker (2017) based on their study showed the anti-inflammatory role of phenolic compounds isolated from *Dendrobii herba* through targeting various inflammation associated cytokines.

Cardiac glycosides

In addition to the above mentioned phytochemicals, another most vital class of natural product that is widely used as therapeutic agent is cardiac glycosides. Cardiac glycosides are bioactive secondary metabolites used as drugs (Morsy, 2017). It comprises aglycone that is linked to sugar molecule. On the basis of lactone ring, cardiac glycosides are classified into two major groups i.e., cardenolides (lactone ring, 5-membered) and bufadienolides (lactone ring, 6-membered) (Skubnik *et al*., 2021). The bufadienolides occurs mostly in animals (Skubnik *et al*., 2021). On the contrary digoxin, digitoxin and oleandrin are the most common cardenolides found in various plants. including *Digitalis* (family Scrophulariaceace). This plant because of its efficacy in congestive heart failure, atrial fibrillation therapy it had been used at the global level (Gerakaris *et al*.,2022). *Digitalis purpurea* is an important source of primary glycosides that are then transformed into digitoxin, gitoxin, and gitaloxin by digipurpidase, an enzyme occurs in leaves of *Digitalis* (Barceloux, 2012).

Cardenolides of aglycone of cardiac glycosides are mostly exploited in cardioactivity(Akinmoladun *et al*., 2014) or anticancerous (Reddy *et al*., 2020). These cardiac glycosides occur in several plant species with its wide range of distribution in angiosperms including *Calotropis procera*, *C. gigantean* (Ibrahim *et al*., 2014; Tripathi *et al*., 2013), *Digitalis* (Gurel *et al*., 2017), *Antiaris toxicaria* (Shi *et al*., 2014), *Nerium oleander* (Botelho *et al*., 2017), *Asclepias curassavica* (Ji *et al*., 2022) etc. Majority of the plants belonging to Apocyanaceae including *Thevetia, Nerium, Apocynum, Cerbera,* and *Strophanthus* are also reported to contain cardenolides with its anticancerous role (Wen *et al*., 2016; Schneider *et al*., 2017; Zhai *et al*., 2022). The mechanism of anticancerous property of cardiac glycosides is possibly a combination of an array of signal transduction pathways (Ainembabazi *et al.,* 2023). Root extracts of *Calotropis procera* had been reported in inhibition of Hep-G2 cells proliferation through apoptosis and through disruption of cell cycle (Mathur *et al*., 2009). Glycosides, Proceraside A isolated from the root barks of *Calotropis procera* were reported to be anticancerous (Ibrahim *et al*., 2014). Cardiac glycosides like Oleandrin from *Nerium oleander* are exploited for the past several years because of its therapeutic properties for treatment of various cardiac abnormalities (Botelho *et al*., 2017). The potentiality of cardiac glycosides mainly relies on its inhibitory activity of Na+/K+-ATPase that makes it an efficient intropic agent for treatment of patients with cardiac insufficiency (Souza *et al*., 2021). Several phytoconstituents including cardiac glycosides was studied in *Vitex negundo* that makes the plant medicinally important (Vijayalakshmi and Rao, 2020). The therapeutic use of cardiac glycosides are summarised in Table 3.

Conclusion

Plants are the potent producers of several bioactive secondary metabolites. These phytochemicals are indirectly involved or take part in metabolism but still play an integral part in survival of the plants. These metabolites because of their efficiency had always been an integral source of drugs worldwide. Since time immemorial the therapeutic effect of plants actually relies on its chemical constituents. Among these the secondary metabolites from the herbals are of greater concern for its critical involvement in treatment of various ailments. The importance of these metabolites lies on the fact that in the present era several problems are faced especially the health issues that bring our attention towards phytochemicals with either no or minimal side effects. Several researches on plant's secondary metabolites had ascended in the past few decades because of its significance in day to day life. However the major challenge is that that there need more research on various aspects of these phytochemicals for better understanding and applications in drug development at the global level in future**.**

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AUTHOR CONTRIBUTION

In the present review, contributions from various published work were collected and all the information were summarised after analysis.

Conflict of Interest

The author declares no conflict of interest.

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