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ANTIPLATELET AYURVEDIC HERBS IN THE MANAGEMENT OF CARDIOVASCULAR DISEASE-A REVIEW

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ABSTRACT

Cardiovascular disease is listed among top ten killer diseases. Antiplatelet drugs reduce the incidence of cardiovascular events by about 20-25% in people with established cardiovascular diseases or at high risk of cardiovascular diseases. The reported antiplatelet ayurvedic drugs described have the potential of improving quality of life while avoiding the side effects of conventional treatment. Out of 16 drugs reviewed *guggulu*, *pippali*, *haritaki* and *sunthi* are the drugs which are frequently prescribed in clinical practice for treating cardiovascular diseases.

Keywords: Antiplatelet drugs, Cardiovascular diseases, Dhamanipratichaya, Guggulu,

INTRODUCTION

Cardiovascular disease (CVD), including heart disease and stroke, is the world's largest killer, claiming 17.1 million lives a year[1]. Among cardiovascular diseases Coronary artery disease (CAD) was the most common cause of death globally in 2013[2]. Current treatment strategies for protecting the heart from ischemic injury includes: beta-blockers, ACE inhibitors, calcium antagonists, nitrates, antiplatelet agents, thrombolytics, antioxidants and free radical scavengers. Antithrombotic is any medication that decreases clots in the body (by dissolving already formed clots or preventing clot formation). This includes the drug classes like anticoagulants, antiplatelets, and thrombolytics. Antiplatelet drugs reduce the incidence of cardiovascular events by about 20-25% in people with established cardiovascular diseases or at high risk of cardiovascular diseases[3].

Platelets are small elements that circulate normally in the bloodstream and help the body defend itself against bleeding and blood loss. Platelets play an important role both in normal hemostasis and in pathological thrombus formation[4]. Although the process of creating a blood clot, which is called thrombosis, is beneficial in a person with severe bleeding, it can also cause problems, particularly when a blood clot forms in the circulation of the heart or brain. A heart attack (myocardial infarction) results when a blood clot interrupts or blocks blood flow to the heart, which starves the heart muscle of oxygen and causes heart muscle cells to die; the same process in the brain causes a stroke[4] .

Drugs that inhibit platelet aggregation are called antiplatelet drugs. They include Thromboxane (TXA_2) synthesis inhibitors like low dose aspirin, Phosphodiesterase inhibitors, Purinergic ($P2Y_{12}$) receptor antagonists, Glycoprotein (GP)II_b/III_a receptor antagonists and other drugs like epoprostenol (PGI_2)[5]. Several large-scale clinical stu-

dies have proved that the inhibition of platelet aggregation results in a significant decrease in mortality and morbidity of ischemic atherothrombotic events. Thus antiplatelet therapy became a key pharmacological method in prevention and treatment of such cardiovascular, cerebrovascular and peripheral arterial diseases[6]. Aspirin and clopidogrel are the most commonly prescribed antiplatelet agents, with a relatively safe profile and efficiency in a variety of clinical conditions.

Ayurvedic treatise documented drugs employed in *Hridroga* (Heart disease). Heart diseases are categorized according to *Dosha* dominance and *Krimi*[7]. Scientific evidences are available on the usefulness of several Ayurvedic drugs in cardiovascular diseases. Several drugs like Arjuna (*Terminalia arjuna*), Harithaki (*Terminalia chebula*), Pushkaramoola (*Inula racemosa*), Pippali (*Piper longum*) are proved to have hypotensive, hypocholestremic, anti-platelet and thrombolytic activities which play a crucial role in the management of cardio-vascular and cerebrovascular disorders. This paper discusses about some of the ayurvedic drugs which are scientifically validated for having antiplatelet activity.

METHODS& MATERIALS

Ayurvedic classics, compendia and journals and internet publications are thoroughly reviewed for compiling the relevant data reported about antiplatelet ayurvedic drugs.

AYURVEDIC ANTIPLATELET DRUGS

1.Andrographis paniculata(Burm.f) Wall.ex Nees

Andrographis paniculata, known on the Indian subcontinent as Chirayetah and Kalmegh is an annual plant, 1-3 ft high, and is one of the most commonly used plants in the traditional systems of Unani and Ayurvedic medicines. In current ayurvedic practice this plant is highly regarded for treatment of jaundice and other liver diseases, fevers and other infections such as dysentery, cholera, gonorrhea, bronchitis and influenza. It is also considered useful in diabetes and an effective remedy for skin disorders. The biologically active chemical constituents of the plant include andrographolide, andrographiside, neoandrographolide and 14-deoxy-11, 12didehydroandrographolide (DDA). A.paniculata has been reported as having antibacterial, antifungal, antiviral, choleretic, hypoglycemic, hypocholesterolaemic, hypotensive, cardioprotective and adaptogenic effects[8]. It is *deepana*, *ruchya* and *amapachana*[9]

Aqueous extract, andrographolide, and DDA inhibit thrombin-induced platelet aggregation in time- and concentration-dependent manners. Extracts with a higher DDA concentration have less inhibitory activity than extracts with lower DDA concentration, indicating the presence of other compounds in the water extract with antiplatelet aggregation activity[10]. Andrographolide inhibits platelet-activating factor (PAF)-induced platelet aggregation in a dose-dependent manner without affecting the biosynthesis of eicosanoids[11].

2. Cassia tora Linn

Cassia tora which is known as chakramarda is an annual bushy herb or under shrub growing upto a height of 1-1.5m[12].Chakramarda is *laghu*, *ruksha* and *vatapittahara* It is *hridya* (beneficial to the heart) and cures kapha ,asthma and kushta[13]. Chrysophanol is the marker constituent of cassia tora. It mainly contains anthraquinone glycosides and flavonoids. The plant is reported to have hypolipidemic,anti inflamma-

tory,antimicrobial,antihepatotoxic,antioxidant and hypotensive activities[14].

The anthraquinone glycosides, gluco-obtusifolin, gluco-chryso-obtusin, and gluco-aurantioobtusin, were found to be platelet anti-aggregatory constituents of the seeds and hence could prove valuable in certain heart problems[15].

3. Commiphora wightii (Arnott) Bhandari

Guggulu is one of the very ancient Ayurvedic drugs, having been first recorded in atharvaveda[16].Guggulu is *deepana*, *medohara* and *rasayana*[17].*Commiphora wightii* contain abundant flavonoids such as E- and Z- isomers of guggulsterone, quercetin, beta-sitosterol, myricyl alcohol, amino acids, myrcene and caryophyllene. Both isomers of guggulsterone (Z and E) demonstrated cardioprotective and antioxidative properties where Z-isomer was more potent than E-isomer in mediating these effects. It acts as anti-inflammatory, antiarthritic, hypocholesterolaemic and hypolipidaemic agent[18].

Guggulsterones have platelet antiaggregant activity as they completely inhibited platelet aggregation induced by adenosine diphosphate, adrenaline or serotonin. Thus guggulipid could play a positive role in the possible protection against coronary heart disease and thrombosis[19].The combination of lipid lowering and antioxidant activities of C.wightii extract makes this a valuable antiatherosclerotic agent[20].

4. Curcuma longa Linn

From times immemorial Haridra is not only a common Indian household condiment, but also a domestic remedy for insect bites,cut and wounds, sore throat, and inflammation and also used as a cosmetic aid for skin[21].According to Charakasamhita it is kushtaghna, lekhaniya and vishaghna[22]. The active constituents of turmeric are the flavonoid curcumin (diferuloylmethane) and various volatile oils, including tumerone, atlantone, and zingiberone. Other constituents include sugars, proteins, and resins. Current research has focused on turmeric's antioxidant, antidiabetic, hepatoprotective, anti-inflammatory, anticarcinogenic, and antimicrobial properties, in addition to its use in cardiovascular disease and gastrointestinal disorders[23].

The antiplatelet activities of *Curcuma longa* rhizome-derived materials were measured using a platelet aggregometer and compared with those of aspirin as antiplatelet agent. The active constituent from the rhizome of Curcuma longa was isolated and characterized as ar-turmerone by various spectral analyses. At 50% inhibitory concentration value, ar-turmerone was effective in inhibiting platelet aggregation induced by collagen and arachidonic acid. However, ar-turmerone had no effect on platelet activating factor or thrombin induced platelet aggregation. In comparison, ar-turmerone was significantly more potent platelet inhibitor than aspirin against platelet aggregation induced by collagen. These results suggested that ar-turmerone could be useful as a lead compound for inhibiting platelet aggregation induced by collagen and arachidonic acid[24].

The best-researched active constituent is curcumin, which comprises 0.3-5.4 percent of raw turmeric. Curcumin inhibit platelet aggregation and enhance the fibrinolytic activity and have strong antioxidant activity[25].

5. Fumaria indica Pugsley

Fumaria indica known as *Parpata* is an annual herb found as a common weed all over the plains of India and Pakistan. Both in Charaka and Susruthasamhita *Parpata* is recommended for treatment of fevers and

blood disorders. The major chemical constituents of the plant include narceimine, tetrahydrocoptisine, narlumidine, methyl fumarate, protopine, bicuculine, and fumariline. The plant is reported to have hepatoprotective, antioxidant, anti-inflammatory, antibacterial and chemopreventive effect[26].

The mode of action of protopine on blood platelet aggregation was investigated in the metabolic system of arachidonic acid and in liberation of platelet activating factor using in vitro experimental models. Protopine inhibited the releases of arachidonic acid and platelet activating factor from platelet membrane phospholipids. Protopine also inhibited the conversion of prostaglandin G2 to thromboxane A2, as well as carboxyheptyl imidazole, a thromboxane synthetase inhibitor. These results indicated that protopine functions both as a phospholipase inhibitor and a thromboxane synthetase inhibitor. It is expected that protopine can be applied for treatment of thrombosis as an antiplatelet drug[27].

6. Litsea glutinosa (Lour) C.B. Robins

Litsea glutinosa known as *medasaaka* is a medium sized evergreen tree. In charaka-samhita it has been classified as *jivaniya, sukrajanana and snehopaga*. It is reported to have antibacterial, antioxidant, anti-inflammatory, antipyretic, hypotensive and chemoprotective activities[28].

Two aporphines (boldine and laurolitsine) and five phenanthrene alkaloids (litebamine, secoboldine, N-cyanosecoboldine, N-methylsecoglaucine and N-methylsecopredicentrine) were evaluated in-vitro for their ability to inhibit platelet aggregation. All seven alkaloids inhibited aggregation of rabbit platelets and inhibited the release of ATP induced by arachidonic acid and collagen in rabbit platelets. The anti-platelet effect of these seven aporphine and phenanthrene alkaloids is mainly a result of inhibition of thromboxane A2 formation; N-methylsecoglaucine has additional antiplatelet activity as a result of increasing the levels of platelet cyclic AMP[29].

7. Nelumbo nucifera Gaertn

Nelumbo nucifera is an elegant long-lived, aquatic plant with stout, creeping underground rhizomes.Various parts of *Kamalam* have been used therapeutically since the samhita period. Several alkaloids all belonging to benzylisoquinoline class (nornuciferine, liensinine, neferine, nuciferine) have been isolated from leaves, seed and seed embryo. From leaves, flower and its receptacle flavonoids have been obtained. It is reported to have hypotensive, antiarrhythmic, hepatoprotective, antioxidant and anti-inflammatory activities[30].

The antiplatelet activity of hydroethanolic extract of both types of flowers (white and pink) was studied using platelet-rich plasma in different concentrations (100-500µg/ ml). Both white and pink Nelumbo nucifera flower extracts showed dose-dependent effective antiplatelet activity with maximum activity at 500µg/ml concentration; prevention of platelet aggregation was 50% of that achieved with standard aspirin. Furthermore, the antiplatelet activity of white flower was relatively high[31].

In connection with the cardiovascular effects neferine has shown to inhibit rabbit platelet aggregation induced by platelet activating factor, collagen or arachidonic acid[32].

8. Nigella sativa Linn

The seeds of Nigella sativa commonly known as black cumin, are used for the treatment and prevention of a number of diseases and conditions that include asthma, diarrhoea and dyslipidaemia[33].It is *deepana* ,

pachana and *kaphahara*[34]. The seeds contain both fixed and essential oils, proteins, alkaloids and saponin. It is reported to have antioxidant, antibacterial, gastroprotective, anti-inflammatory, hypotensive and anti-cancer activities[35].

Methanol soluble portion of the *N.sativa* seed oil displayed inhibitory effects on arachidonic acid (AA) induced platelet aggregation and blood coagulation in in vitro studies. By bioactive assay of AA-induced platelet aggregation, the methanol soluble part was purified to isolate a new compound 2-(2-methoxypropyl)-5-methyl-1,4-benzenediol and two known compounds, thymol , carvacrol , having very strong inhibitory activity[36].

9. Picrorhiza kurroa Royle ex Benth

Picrorhiza kurroa (*Katuki*) is a well-known herb in the Ayurvedic system of medicine and has traditionally been used to treat disorders of the liver and upper respiratory tract, reduce fevers, and to treat dyspepsia and chronic diarrhea[37].It is *laghu, deepana, bhedana* and *hridya*[38]. Kutkin is the active principal of *Picrorhiza kurroa* and is comprised of kutkoside and the iridoid glycoside picrosides I, II, and III. Other identified active constituents are apocynin, drosin, and nine cucurbitacin glycosides[39]. Different extracts of Pkurroa rhizomes have shown to exhibit hepatoprotective, antioxidant, anti-inflammatory, antidiabetic and cardioprotective action[40].

Androsin a chemical constituent of the plant rhizomes has been reported to prevent allergen and platelet activating factor induced bronchospasm in guinea pigs[41].

10. **Piper longum Linn**

Pippali is highly valued in Ayurveda for treating several clinical manifestations, mostly relating to indigestion, fever, asthma and cough. In modern ayurvedic practice pippali is considered as anti-inflammatory, analgesic, antigout, hepatoprotective, cardiotonic and cerebral vasodilator[42].

In a study the inhibitory effects of four acidamides, piperine, pipernonaline, piperoctadecalidine, and piperlongumine, isolated from the fruits of *Piper longum* on washed rabbit platelet aggregation were examined. All of the four tested acidamides showed dose-dependent inhibitory activities on washed rabbit platelet aggregation induced by collagen, arachidonic acid (AA), and platelet-activating factor (PAF), except for that induced by thrombin. Piperlongumine, in particular, showed stronger inhibitory effects than other acidamides to rabbit platelet aggregation induced by collagen, AA and PAF[43]

11. Psoralea corylifolia Linn

Psoralea corylifolia known as bakuchi is highly valued in ayurveda for treatment of skin diseases and hence the name K*ushtaghni*. It is *kaphapithahara*, *sara*, *rasayana* and *hridya*[44]. The plant is pharmacologically studied for its chemoprotective, antioxidant, antimicrobial, antidiabetic and anti-inflammatory properties. Isobavachalone a contituent of *Psoralea corylifolia* showed effects on cardiovascular system[45].

The MeOH extract of the seeds of *Psoralea corylifolia* was found to inhibit the aggregation of rabbit platelets induced by arachidonic acid, collagen, and platelet activating factor. Bioassay-directed fractionation led to the isolation of three flavonoids, isobavachalcone, neobavaisoflavone, and bavachin.Isobavachalcone and neobavaisoflavone inhibited platelet aggregation[46].

12. Pueraria tuberosa DC

Pueraria tuberosa (Vidari) is highly valued in Ayurvedic classics as a restorative, tonic

and rejuvenator. It is also considered cardiotonic, laxative and useful in disorders of liver and spleen. Various extracts of the tubers have been shown to possess antifertility activity. The plant is also reported to have hepatoprotective and hypoglycemic activity. Total flavanoids mixture has been demonstrated to exhibit coronary vasodilatory effect[47].

Puerarin at .25,.5,1,3mg/ml inhibited ADP induced rat, rabbit and sheep platelet aggregation in vitro. Puerarin has been shown to inhibit release of serotonin from platelets. This has a bearing on the treatment and prevention of angina pectoris and myocardial infarction[48].

13. Rauvolfia serpentina L.Benth ex Kurz

Rauvolfia serpentina has been described as one that slows heart and induces sleep[49]. Since 1949, after the English publication of a clinical report on Rauwolfia serpentina therapy in fifty cases of essential hypertension, the plant has gained universal acclamation as a useful therapeutic weapon in high blood pressure states[50]. The major alkaloid present in root, stem and leaves of the plant is Reserpine. The minor alkaloids present in the plant are Ajmalicine, ajmaline, isoajmaline, ajmalinine, chandrine, rauwolfinine, renoxidine, rescin-namine, reserpiline, reserpin, reserpinine, sarpagine, serpentine, serpentinine, tetraphyllicine, yohimbine, 3-epi-ayohimbine[51].

The in vitro and in vivo effects of ajmaline and its derivatives on platelet aggregation and platelet-activating factor (PAF) induced death in rabbits was studied. Ajmaline and acetyl ajmaline selectively inhibited PAF-induced aggregation in a concentration related manner. Weak or no inhibition of aggregation was observed when ADP, collagen or arachidonic acid was used as aggregating agents. Similarly ajmaline or acetyl ajmaline also inhibited the lethal effects of PAF in the rabbit. PAF (8-11 microg/kg i.v.) caused sudden death in rabbits due to platelet aggregation and cardiac failure. Pretreatment of rabbits with ajmaline protected conscious rabbits from PAF induced death. Since PAF is a powerful inducer of platelet aggregation via stimulation of specific PAF membrane receptors, our data is suggestive that ajmaline (an anti-arrhythmic agent) could emerge as a new class of PAF antagonists[52].

14.Rubia cordifolia Linn

Rubia cordifolia known as manjishta is used for the treatment of burns and has been included in the plant group priyanguvadi by Susruthasamhita. It is considered beneficial in deranged Pitta, ulcers, bone fractures and dysentery especially when stools have much mucus. The plant is scientifically validated for its antioxidant, antitussive, antibacterial and uterine stimulant activities[53].

The effect of the partially purified fraction of the whole plant has been studied on rabbit platelets. It inhibits the platelet aggregation induced by PAF (platelet activating factor) but not thrombin. It also inhibits the binding of 3H-PAF to the platelets in the dose-dependent manner. Thus it appears that R.*cordifolia* inhibits action of PAF at its receptor level either by its blocking or by desensitization[54]

15. Terminalia chebula Retz

Harithaki is one of the most valued drugs of Ayurveda and is much used both as a purgative band for treatment of sprue. It is essentially considered as a tonic and restorative. The plant has been demonstrated to possess multiple pharmacological and medicinal activities, such as antioxidant, antimicrobial, antidiabetic,hepatoprotective,antiinflammatoyantimuta

genic,antiproliferative,radioprotective, cardioprotective, antiarthritic, anticaries, gastrointestinal motility and wound healing activity[55].

An investigation was carried out to assess the anti-platelet activity of crude methanolic extracts of *Terminalia chebula* Retz. Fruits. The crude extracts exhibited potent platelet aggregation inhibition activity in a dose-dependent manner at concentration range (1 to 10 mg/ml) [56].

16 Zingiber officinale Rosc.

Ginger is a household remedy for several gastrointestinal disorders and has been classified as carminative, promoter of digestion, anticolic and curative of piles and haemorrhoids. Different extracts of ginger is reported to have, antibacterial, antioxidant, antiulcer, anti-inflammatory, cardioprotective and hypocholesterolaemic activities[57].

In a study some of the isolates from *Z.officinale* were subjected into the evaluation of their antiplatelet aggregation and vasorelaxing bioactivities. Among the tested compounds, [6]-gingerol and [6]-shogaol exhibited potent anti-platelet aggregation bioactivity. In addition, [10]-gingerol inhibited the Ca^{2+}-dependent contractions in high K^+ medium[58]

DISCUSSION

Platelets play a crucial role in thrombosis, inflammation, immunity and atherogenesis. In the case of vascular endothelial damage, the first haemostatic reaction is vasoconstriction. Thereafter, the platelets come into action and the coagulation system is activated. Through disruption of the endothelial layer of the vessel wall, tissue factor is exposed, initiating the coagulation cascade, resulting in thrombin formation. Also subendothelial collagen and Von Willebrand factor are exposed to the flowing blood. Following this event, platelets start to adhere to collagen and Von Willebrand factor through their respective receptors, forming a platelet monolayer covering the damaged part of the vessel wall. This monolayer serves as a base for thrombin generation and platelet aggregation. Adhered platelets undergo shape change, form podocytes, and start to secrete thromboxane A2 (TXA-2) and their granule contents, such as adenosine diphosphate (ADP). Through their specific receptors on the platelet surface, thrombin, TXA-2, ADP and other substances help recruit and further activate platelets at the site of endothelial damage. Activated platelets express the glycoprotein IIb/IIIa receptor, which is the receptor for fibrinogen. This receptor is essential for irreversible aggregation for which fibrinogen serves as the glue between the platelets[59]. . In cardiovascular disease, abnormal clotting occurs that can result in heart attacks or stroke. Blood vessels injured by smoking, cholesterol, or high blood pressure develop cholesterol-rich build-ups (plaques) that line the blood vessel; these plaques can rupture and cause the platelets to form a clot. Even though no bleeding is occurring, platelets sense the plaque rupture and are confused, thinking that an injury has taken place that will cause bleeding. Instead of sealing the vessel to prevent bleeding as would occur with a cut, a clot forms in an intact blood vessel, causing a blockage of blood flow. Without blood, a portion of the heart muscle can die, leading to a heart attack[60].

In modern medicine treatment of IHD involves expensive and chronic drug therapy or equally expensive interventional procedures such as thrombolytic therapy and surgical recanalization. Reperfusion injuries

and undesired side effects of the drugs are the major drawbacks of conventional therapies[61].

According to ayurveda heart disease is the outcome of faulty diet and stressful lifestyle which leads to an ama state leading further to *dhamanipratichaya* resulting into angio-obstruction and aggravation of vata dosha resulting in chest pain and angina.[61]*Dhamanipratichaya* described under Kaphaja Nanatmajavikara, is akin to atherosclerosis. The pathogenesis begins with the morbid accumulation of *kapha* and *medas* in the blood. This excess of *kapha* and *medas* in the blood is referred as *shonitabhishyandana*. Thus morbid *shonita* circulating in the *dhamani* predisposes to *upalepa* or adherence of *kapha* and *medas* within the wall of the dhamani. Due to the abnormal accumulation of the *kapha* and *medas* within the wall of the *dhamani* leads to remodeling of the *dhamani*. Narrowing, thickening, tortuosity and lack of *distensibility* is the change that occurs in the *dhamani* due to pathological remodeling mediated by the adherence of *kapha* and *medas*. This pathological change in the *dhamani* is known as *dhamanipratichaya*[62,63].

According to chakrapani all the measures intended to subside vata and kapha may cure Hridroga[64]. Among the above mentioned drugs *Chakramarda*, *Haridra*, *Medasaaka, Upakunchika*, *Pippali*, *Bakuchi*, *Sarpagandha*, *Shunthi* are *Kaphavatahara*. All the drugs mentioned so far are kaphahara except vidari which is vatapithahara. Haridra and katuki have lekhana(scrapes the excessive kapha and medas) property. Guggulu and chakramarda are medohara. Drugs having deepana property like *guggulu*, *pippali*, *katuki*, *harithaki*, *shunthi* and *medasaaka* help in kindling the digestive fire. *Deepana*, *Pachana*, *kaphahara* and *medohara* properties of the drugs help in correcting the pathogenesis of atherosclerosis. Ayurveda advocates prevention first and cure next. The preventive aspects include changes in ahara, vihara and oushadha.

Oxidative stress appears to play a key role in the pathogenesis of atherosclerosis.Agents that prevent the oxidation of low-density lipoprotein have reduced the development and progression of this disease in a range of in vitro experiments and animal models. All the plants listed here are reported for their antioxidant activities[65]. The combination of lipid lowering and antioxdant activities makes a valuable antiatherosclerotic agent.

The ayurvedic drugs described here have the potential of improving quality of life while avoiding the side effects of conventional treatment. The widespread use of such drugs in cardiovascular diseases can improve the quality of life in individuals and potentially save millions of lives.

CONCLUSION

Cardioprotection includes "all mechanisms and means that contribute to the preservation of the heart by reducing or even preventing myocardial damage". Several ayurvedic drugs like *Arjuna*, *Guggulu*, *Pushkaramoola* are scientifically validated as effective cardioprotectives. Antiplatelet drugs play a significant role in the prevention and treatment of cardiovascular diseases. Further researches on Ayurvedic antiplatelet drugs should be carried out to prove their safety and efficacy.

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