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RESEARCH ARTICLE

A PHARMACOLOGICAL STUDY OF ARJUNA (TERMANALIA ARJUNA) – A BRIEF STUDY

***Shreedevi Huddar, Ullegaddi N.S. and Kambale Vaishalee**

HOD and prof. Dept of Dravyaguna; Prof. Dept of Dravyaguna; P.G. Scholar Dept of Dravyaguna

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****Corresponding author: Shreedevi Huddar,***

ABSTRACT

Terminalia arjuna, commonly known as arjuna, belongs to the family of Combretaceae. Its bark decoction is being used in the Indian subcontinent for anginal pain, hypertension, congestive heart failure, and dyslipidemia, based on the observations of ancient physicians for centuries. The utility of arjuna in various cardiovascular diseases needs to be studied further. Therefore, the present review is an effort to give a detailed survey of the literature summarizing the experimental and clinical studies pertinent to arjuna in cardiovascular disorders, which were particularly performed during the last decade. Systematic reviews, meta-analyses, and clinical studies of arjuna were retrieved through the use of PubMed, Google Scholar, and Cochrane databases. Most of the studies, both experimental and clinical, have suggested that the crude drug possesses anti-ischemic, antioxidant, hypolipidemic, and antiatherogenic activities. Its useful phytoconstituents are: Triterpenoids, β-sitosterol, flavonoids, and glycosides. Triterpenoids and flavonoids are considered to be responsible for its beneficial antioxidant cardiovascular properties. The drug has shown promising effect on ischemic cardiomyopathy. So far, no serious side effects have been reported with arjuna therapy. However, its long-term safety still remains to be elucidated. Though it has been found quite useful in angina pectoris, mild hypertension, and dyslipidemia, its exact role in primary/secondary coronary prevention is yet to be explored.

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INTRODUCTION

Ayurvedic classics treasures a rich repertory of medicinal plants used for the treatment, management and/or control of different types of diseases. Knowledge about the healing property of medicinal plants used in Ayurvedic therapeutics mentioned in classics is a result of astute clinical observations made over centuries. Details about their properties and therapeutic applications are available in ancient scriptures like Vedas, Samhitas and Puranas. Compilations of later periods that are called Nighantus also contain enormous amount of information. The current global trend towards utilization of plant-derived natural remedies has, therefore, created a dire need for accurate and up to date information on the properties and uses, efficacy, safety and quality of medicinal plant products. Hence, the review of traditional medicinal plant and their formulations mentioned in Ayurvedic classics is crucial in present era. Terminalia Arjuna (Roxb.) influence in Ayurvedic system of medicines. In Rigveda, the word 'Arjuna' is used either to indicate the white colour or one of taintless fame and glow like silver. It may be the first reference of Arjuna used as medicine stated in chief or principle sutra volume of Atharvaveda, Kaushiksutra (400- 300 B.C.). Further synonyms and properties of Arjuna are mentioned in Bhavprakash Nighantu. Later on Chakradatta, the great ancient physician, recommended uses of Arjuna bark in form of decoction with milk (Kshirpaka) or as a ghrita (a preparation with ghee). Since, detailed combined assessment on modern aspects as well as Ayurvedic classical preparations of different formulations of Arjuna along with scientific symposium were not available on one platform during extensive literature search hence it was thought worthwhile to undertake detailed review study.

Plant Profile

ARJUNA (Terminalia arjunaRox.)

1. Taxonomic Classification:
2. Kingdom: Plantae
3. Sub-kingdom: Tracheobionta
4. Divisioni: Magnoliophyta
5. Subdivision: Spermatophyta
6. Class: Magnoliopsida
7. Order: Myrtales
8. Family: Combretaceae
9. Genus: Terminalia
10. Species: T. arjuna
11. Zoological name: Terminalia arjuna

Morphology

Arjuna is a large deciduous tree with spreading crown and drooping branches.It attains a height of up to 35 m.Its bark is thick, grey to

pinkish green, smooth, thin, coming off in irregular sheets.Leaves are usually sub-opposite, 10–15 cm long, and 4–7 cm broad; base is rounded or heart shaped, often unequal sided; veins are reticulate.

Floral Charecterstics: Flowers are sessile and occur in simple or Panicled spikes Calyx is glabrous and has five short triangular lobes. Fruit is a fibrous-woody drupe, about 2.5–5 cm in size. It is dark brown when mature and has five hard, projecting, veined wings. Flowering occurs from May to June, while fruits mature from January to March.

Distribution: The species is common in mixed dry deciduous tropical forests throughout the greater part of India. It is often found along the water courses, cultivated elsewhere as avenue tree It is a common avenue tree in many cities, such as Delhi.

Pharmacological Activity of *Arjuna:* Free radicals are molecular species that donate or accept electrons from other molecules and thus act as oxidants or reductants. These free radicals are unstable and highly reactive (hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, nitric oxide radical, hypochlorite, and peroxynitrite radical), resulting in the damage to cells as well as the disruption of homeostasis. In the human body, free radicals are generated as a result of a few essential metabolic processes, such as exercise and ischemia/reperfusion injury, or due to exposure to harmful radiation sources (such as x-rays, UV, and others) and toxic chemicals (such as cigarette smoke or ozone fumes, to name a few) Antioxidants are the chemicals that counteract and stabilize the excessive production of free radicals and enhance the immune response. These are generally produced inside the body, or they can be given as a supplement to prevent diseases. Natural herbs are considered to be a rich source of these antioxidants. The phytochemical constituents that are mainly responsible for the antioxidant property are the phenolic compounds. The major flavonoid and phenolic compounds in the leaves of TA include gallic acid, apigenin, luteolin, quercetin, epicatechin, ellagic acid, and 1-*O*-β-galloyl glucose, and they are identified as the sources for TAs antioxidant activity. Plant biomolecules act as electron donors, reductants, singlet oxygen quenchers, and chelate metal ions to exhibit their antioxidant property. The mechanism behind phenolic compounds' exhibiting the antioxidant property is that phenolic compounds in plants possess one or more aromatic groups along with one or more hydroxyl groups. The antioxidant potential of the phenolic compounds is due to the conjugation and side chains of the aromatic rings with the generated free hydroxyl radicals. The another antioxidant mechanism in which flavonoids exerts its property is through scavenging the hydrogen peroxide radicals. For instance, hydrogen peroxide is mainly formed by superoxide dismutase within the cells. The flavonoids donate electrons or protons to convert the produced hydrogen peroxide into water. The equation represents the possible mechanism of hydrogen peroxide radical scavenging activity of the quercetin (flavonoid) molecule. The role of solvents plays a key role in extracting the right phytochemicals with antioxidant properties. For instance, in the case of phytochemical extraction from TA leaves, the aqueous extraction was found to have the highest free radical scavenging properties when compared to other extraction processes involving other solvents, such as benzene, acetone, petroleum ether, hexane, and chloroform. The chloroform extracts non-polar compounds, such as triterpenes and lipids, and the n-butanol extracts mid-polar compounds, such as oxidized catechins and flavanol glycosides, while highly polar compounds, such as tannins and polyphenols, reside in water. Likewise, the methanolic extract of TA bark also exhibits high antioxidant potential, which is mainly due to its flavonoid content. Methanol and ethanol are the solvents generally preferred to extract molecules with antioxidant properties.

However, ethanol is highly preferred due to its low levels of toxicity. The polarity and increased solubility of many antioxidant molecules in methanol make it an ideal solvent chemically, although its toxicity limits its applications. With an increase in the concentration of the extract, there is an increase in the reducing power, which is a key indicator in determining the antioxidant activity. Scavenging of hydrogen peroxide (H_2O_2) is important because it gives hydroxy radicals to cells, which are toxic to cells. It can be neutralized by elevating the dosage level of phytochemical extracts. The phenolic compounds will scavenge the hydrogen peroxide by donating one electron and neutralizing it, leading to the formation of water. The methanolic extract exhibits the highest antioxidant activity, followed by ethanolic extracts, while the lowest activity was found in the n-hexane solvent.

Anti-Inflammatory: Inflammation is usually caused by infection, xenobiotics, and a weak immune response. The inflammatory response involves the recruitment of macrophages and neutrophils in the initial phase, which secrete different mediators to cause acute inflammation. Nitric oxide is a key mediator that induces inflammation through the expression of inducible (iNOS). Plant flavonoids inhibit nitric oxide (NO) production and downregulate the expression of iNOS (nitric oxide synthase). Flavonoids also inhibit the biosynthesis of prostaglandins by inhibiting the enzymes cyclo-oxygenase and COX-1 and 2 at the molecular level. The pro-inflammatory cytokines are also inhibited by these flavonoids. The anti-inflammatory study on the TA leaf was reported for its methanolic extract. The methanolic extract of the leaf efficiently reduced the carrageenan-induced paw edema. The possible mechanism reported was the inhibition of COX enzymes, which leads to the inhibition of prostaglandin synthesis. The commercially available TA capsules (containing TA bark extract) were also studied for their anti-inflammatory activity in paw edema models developed using formalin and carrageenan.

It was reported that the plausible anti-inflammatory mechanism could be any of the following:

Blocking the biosynthesis of proinflammatory mediators (COX II); Inhibiting the release of mediators (e.g., histamine, a potent inflammatory mediator); blocking the mediator-receptor (e.g., leukotriene receptor, an inflammatory mediator) interactions; and Immune stimulation (e.g., myeloid cell maturation). It was also reported that the TA extract increased the amount of antioxidant enzymes (superoxide dismutase and catalase) as well as reduced the glutathione content, which as a whole results in the enhancement of anti-inflammatory activity. For instance, during inflammation, the neutrophils are recruited at the site to initiate the release of ROS and chemokines. The release of superoxide anions activated the endothelial cells, generated chemotactic mediators (leukotriene B4), and upregulated adhesion molecules that increase neutrophil infiltration. The neutrophils under oxidative stress generate reactive oxygen species, where the antioxidant enzyme SOD acts as an endogenous cellular defense system and degrades the superoxide into oxygen and hydrogen peroxide, where the generation of hydrogen peroxide Activates the caspases three, eight, and nine, to induce neutrophil apoptosis.

Cardio Protective Property: TA has always been considered a cardio tonic plant since the ancient era and is currently gaining importance in the treatment of various cardiac disorders. The alcoholic extract of TA includes lactones, flavonoids, phytosterol, phenolic compounds, glycosides, and tannins that have excellent antioxidant, antihyperlipidemic, and cardio protective properties. The cardiovascular disease is caused due to many factors, such as hyperlipidaemia, hyperglycaemia, inflammatory response, coagulation factors, increased platelet activation, smoking, and oxidative stress. The cardio-protection is studied using the gemmomodified (plants at growing stage) extract and the methanolic extract of the TA bark. The HPLC analysis of the extracts revealed that bark has a higher concentration of flavonols (quercetin, myricetin, and kaempferol), flavanole (catechin), and phenolic acid (gallic acid, *P. coumaric*, and ferulic acid). The mechanisms behind TAs cardiac protection properties are as follows:

1. Flavonoids present in them reverse endothelial dysfunction and reduce the arterial pressure by increasing the vasorelaxation process.
2. The flavonoids also scavenge the free radical species through scavenger receptors and help in the uptake and elimination of oxidized modified low-density lipoprotein (OM-LDL)(OM-LDL is a chemically modified LDL that results in endothelial injury to initiate atherosclerotic plaque formation .
3. Regulation of platelet activity and by inhibition of platelet aggregation as depicted in.

Both the bark extract as well as the gemmomodified extract have potent properties to cure induced myocardial infarction. The aqueous ethanolic extract of bark has been studied for various factors that cause chronic heart failure. For instance, lipids play a vital role in cardiovascular diseases since the alteration in lipid metabolism manipulates cardiac functions by affecting the structure, stability, and composition of the cell membrane, which in turn leads to cell death followed by ischemia. This extract helps by reducing the LDL and increasing the HDL, which proves the lipid-lowering properties of the plant extract. In other instances, the cell membrane of the myocardial cells gets damaged, which results in the leakage of the enzyme, creatine kinase. The treatment with aqueous ethanolic extract maintains the membrane's integrity by increasing the level of creatine kinase and thereby stopping the leakage of enzymes.

Another study revealed that the cardio-protection properties of TA are due to the following reasons:

(a) Through the antioxidant properties of tannins and
(b) Through activating the physiological antioxidants inside the body by the Oleanane triterpenoids.

Anti–Atherosclerotic: Atherosclerosis is an inflammatory vascular disease caused by the deposition of cholesterol in the arterial wall. Atherosclerosis is one of the major causes of cardiovascular diseases. The key factors responsible for plaque formation are the stimulation and differentiation of monocytes in the blood stream, followed by the low-density lipoprotein uptake by macrophages to form the foam cells. The different ethanolic derivatives of TA demonstrate the presence of phenolics, tannins, triterpenoids, saponins, anthraquinone glycosides, alkaloids, and flavonoids and confirm the anti-hyperlipidemic activity through its anion exchange property. The main mechanism behind the anion exchange property is that the anions of phytochemicals in the plant bind with the bile acid anions in the intestine and convert cholesterol into bile acid, which is then excreted in stool and leads to a decrease in the serum LDL cholesterol level. arjunic acid and arjunoglycoside (I, II, III and IV) undergo a drug-metabolizing cascade, produce some active molecules, and are responsible for lipid-lowering activity. Tannins also are found to be helpful in depleting the lipid activity. There is another mechanism reported that uses the aqueous bark extract of TA to treat atherosclerosis. The medicinal herbs are rich sources of ligands for nuclear receptors, such as the peroxisome proliferator-activated receptor α (PPARα) and the peroxisome proliferator-activated receptor γ (PPAR γ). Provides a schematic representation of the mechanism of TA to inhibit NF-κβ and thus prevent plaque progression. Treatment with this extract activates the PPAR-γ by inhibiting the NF-κβ, which reduces the action of Interleukin 18 (IL 18) and also inhibiting the expression of other cytokines, chemokines, and adhesion molecules, and finally stops the plaque progression. Additionally, the TA extract also soothes the inflammatory cascade through pleiotropic activation of PPAR–γ and LXR (liver X receptors)–α as PPAR–γ upregulates the LXR–α and promotes cholesterol efflux and it also regulates the scavenger receptor (CD36) activation which helps in uptake of oxidized LDL in foam formation. The reduced expression of matrix metallopeptidase 9 (MMP 9) is also another possible mechanism to reduce atherosclerotic plaque formation.

Anticancer: Cancer is a life-threatening disease that often results in death. The current treatment strategies include primarily surgery, radiotherapy, and chemotherapy, with few adjuvant therapies. The above-mentioned treatment strategies are very harsh on patients, resulting in pain and serious side-effects, such as the loss of hair and severe pain, to name a few. In order to reduce the side-effects of the existing cancer treatment strategies, herbal medicines are currently much preferred. These phytoconstituents are reported to have excellent properties, such as (a) methyltransferase inhibition, (b) DNA damage prevention or antioxidant properties, (c) histone deacetylases inhibition, and (d) mitotic disruption that prevents cancer development. The secondary metabolites, such as polyphenols, brassinosteroids, and taxol, are found to possess anti-cancer activity. In TA, the high content of tannin and polyphenols is mainly responsible for the anticancer activity. Besides the phytoconstituents, the taxol is also produced from Pestalotiopsis terminaliae, an endophytic fungus found in the leaves of TA.

Taxol is a highly preferred drug for the treatment of human malignant cancers. In cancer cells, microtubule formation plays a major role in mitosis, motility, cell shape, and cellular response. The microtubule is comprised of α and β tubulin heterodimers which helps in the assembly of microtubule network through polymerization. α and β tubulin are the globular proteins with three functional domains (N-terminal, C-terminal, and an intermediate domain). Taxol binds with the β-tubulin on the intermediate domain to suppress the spindle formation and deploy the mitotic division, thereby arresting the cell division of the malignant cells. TA extracts are also tested in colon and liver cancer cell lines for their anti-cancer activity. It was found that the bioactive molecules in the TA leaf extract destroy the cancer cells either by activating apoptosis or through the inhibition of the growth regulators. The anticancer activity of TA bark is reported to be due to the presence of phenolic compounds that interact with target DNA through signaling pathways, as depicted in and block the sites involved in the electrophilic attack by reactive carcinogenic moieties.

DISCUSSION

As outlined above, results from various*samhitas* and *nighatus* studies indicate *arjuna* possesses many qualities, including *Kustha,Vataroga, Dipan, Pachan, Jwara,* Osteoporosis, Pregnancy to infertile women, strength, anti-inflammatory, antitumor, hypoglycemic and immunomodulatory properties, as well as exerting an influence on the endocrine, nervous, and cardiopulmonary systems. According to the *samhitas* and *nighantusarjuna* used in the various form or medium. The review indicates that *arjuna* may be useful in many ailments. Including arthritis and other musculoskeletal disorders, and hypertension. There are a few preliminary studies available on the effects of *arjuna* on the immune system, central nervous system, hemopoetic system, and general growth promotion to form a basis for further studies but not enough evidence to provide a firm scientific basis for definitive therapeutic uses.

CONCLUSION

Samhita and *Nighantus* are the basic literature for Understand and identification of different medicinal plants. On review of *Arjuna* in different *samhita*and *nighantus* we find the different synonyms and properties along with useful formulations and their medicinal action on various pharmacological activities.

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