

Pharmacognosy of *Azadirachta indica* and possible use in COVID- 19: a review

Análisis de la farmacognosia de *Azadirachta indica* y su posible uso en el COVID-

19

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ABSTRACT

Neem is the most useful traditional medicine as a source of many medicinal agents in Indian society, and it grows well in tropical and semi-tropical countries. Any part of the neem tree is used in the indigenous medicine scheme, viz. Bark, berries, berries, seeds and extracts. Its extracts have antiviral, antibacterial, antifungal, anthelmintic, anti-allergic, anti-dermal and anti-inflammatory properties. Neem is also referred to as "Free Tree of India," "Wonder Tree," "Nature Drug Store," "Divine Tree," "Heal All" and "Panacea of All Diseases." In this period, special focus should be put on the prevention of both human and animal diseases using non-toxic herbal products. There is a lot of potential for greater use of this wonderful facility. Each part of the neem tree has certain medicinal properties. In the last five decades, apart from the chemistry of neem compounds, substantial development has been made concerning the biological function and medicinal applications of neem. It is now known to be a valuable source of specific natural products for the production of medicines against different diseases and also for the development of industrial products. this review tries to provide the importance of this ancient plant importance with the risk factor. Current time COVID -19 pandemic its use in sanitisers, hand wash but *Azadirachta indica* pharmacognosy ability does not completely utilize its beneficial properties.

Keywords: ayurveda, pharmacological activity, *Azadirachta indica*, traditional medicine, COVID -19

RESUMEN

El neem es la medicina tradicional más eficiente y fuente de varios agentes medicinales en la sociedad india, además, crece bien en países subtropicales y tropicales. Cada parte del árbol de neem es utilizado en el plan

medicinal indígena, como la corteza, frutos, semillas y extractos. Este último, tiene propiedades antivirales, antibacterianas, antifúngicas, antihelmínticas, antialérgicas, antidérmicas y antiinflamatorias. Otros nombres para el neem son: “árbol libre de la India”, “árbol milagroso”, “farmacia natural”, “árbol divino”, “sanador de todos” y “panacea de todas las enfermedades”. Actualmente, se debería prestar mucha atención a la prevención de enfermedades humanas y animales, utilizando productos a base de plantas no tóxicas, ya que hay un gran potencial para un mayor uso de este maravilloso árbol. Cada parte del árbol de neem tiene ciertas propiedades médicas. En las últimas cinco décadas, aparte de la química de los compuestos del neem, se han realizado avances sustanciales respecto a la función biológica y los usos medicinales de esta planta. Además, es conocida por ser una fuente valiosa de productos naturales específicos para la producción de medicinas contra diferentes enfermedades y también para el desarrollo de productos industriales. Este análisis intenta proporcionar la importancia de esta planta ancestral y el factor de riesgo. En el tiempo de la pandemia de COVID-19, el neem se utilizó en productos de lavado de manos y desinfectantes, sin embargo, no se utilizaron completamente todas las propiedades benéficas de la farmacognosia de *Azadirachta indica*.

Palabras clave: ayurveda, actividad farmacológica, *Azadirachta indica*, medicina tradicional, COVID-19.

INTRODUCTION

For thousands of years, herbs have been used by many cultures for their medicinal value. Herbal treatment is very common because it is readily available, inexpensive and less toxic. 'Neem tree, *Azadirachta indica*, is a tropical evergreen tree particularly suited to semi-arid conditions and thrives even in the poorest soil, with rainfall as low as 18 inches per year and temperatures as low as 50 Celsius. It is proclaimed "Tree of the 21st century," "Divine tree," "Life giving tree," "Nature drug store," "Village pharmacy," and "Panacea of all diseases." It has tiny flowers, white flowers with sweet jasmine-like fragrance, edible fruits, pinnate leaves with a very bitter taste and garlic-like scent. Herbs have been used for thousands of years by many cultures for their medicinal value. Herbal therapy is very common because it is readily available, inexpensive and less toxic [1]. *Azadirachta indica* (neem) is a medicinal plant widely distributed in our subcontinent during all seasons. The advantageous properties have been in existence for thousands of years. Neem is also known as VEP A in Telugu, eppilai in Tamil, Aaru Veppila/Veppila in Malayalam, Bevu/Olle Bevu in Kannada, Nim in Hindi, Nim/Nimba Pata in Bengali, Limba in Gujarati and Kadulimb in Marathi. Indigenous use of *A. Indica* (the common name in Hindi is 'Neem') leaves in various parts of India are widely distributed to treat gastrointestinal disorders such as diarrhea and cholera (Thakurta et al. 2007) [2]. Any part of the neem tree has health-promoting benefits with pharmaceutical and pesticide-control properties. Azadirachtin compound in neem has been recognized as an effective insecticide that is biologically selective [3].

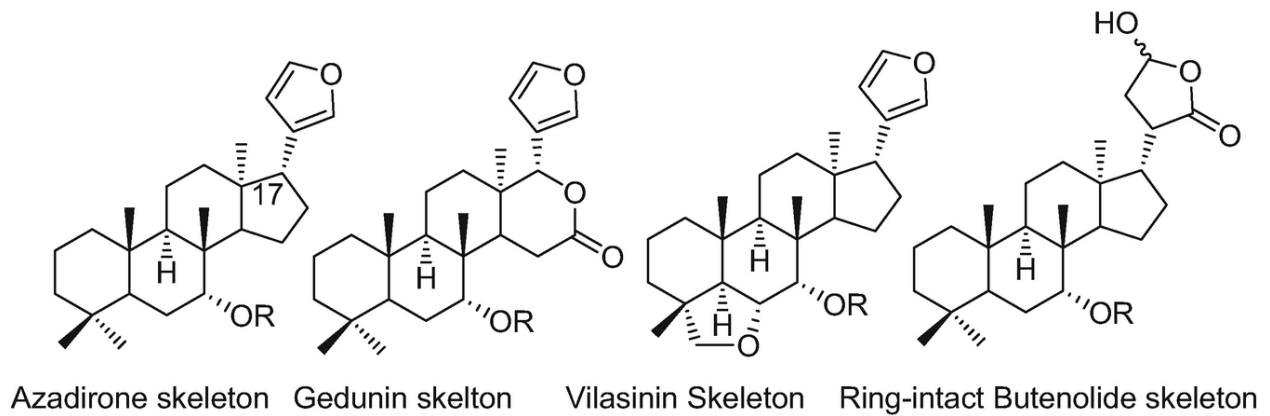
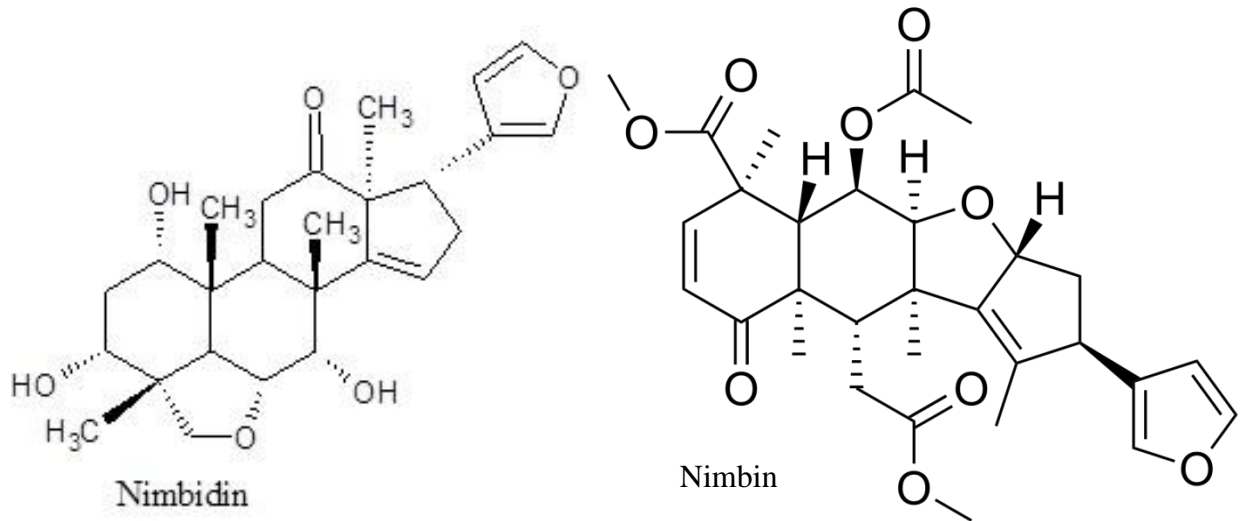
The medicinal properties of Neem leave in the ayurvedic medicine system are well known in Bangladesh, India and Pakistan. Over the last decade, the anticancer properties of neem have been established. A variety of scientific angles have been explored in detail. Neem with medicinal properties rejuvenates the liver and normalizes its function. The Poison Accumulated in the liver is periodically expelled with continuous neem intake. This one, it helps to control the varying levels of blood cholesterol and blood sugar. Neem is also contributing to rejuvenate skin. Diabetes patients are more susceptible to itchy skin and dry skin. Daily, regular using neem to help the skin resolve this condition slowly [4, 5].

Table 1: Botanical classification of Neem Plant

Kingdom	Plantae
Phylum	Vascular plant
Class	Magnoliopsida
Order	Rutales
Suborder	Rutinae
Tribe	Melieae
Family	Meliaceae
Subfamily	Melioideae
Genus	Azadirachta
Species	Indica

Source: (Girish and Shankara 2008.) [5]

Over than 135 compounds have been isolated from different parts of neem with chemical and structural diversity. These compounds have been classified into two main classes: isoprenoids (like diterpenoids and triterpenoids comprising protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasin type compounds and C-secomeliacins such as Nimbin, salanin and azadirachtin) and nonisoprenoids, proteins or amino acids and carbohydrates (polysaccharides), sulphur compounds (Biswas et al., 2002) [7]. Nimbidine, a major bitter part of a seed kernels oil. Indica has shown many biological activities. Some tetranortriterpenes, including nimbin, nimbinin, nimbidinin, nimbolide and nimbidicacid, have been isolated from crude components [6].



Pharmacological actions: abortifacient, analgesic, anthelmintic, antibacterial, antibacterial, antiulcer, antifertility, anti-filarial, antifungal, anti-hyperglycemic, anti-inflammatory, antiviral, antimalarial, diuretic, anti-nematodal, antipyretic, antispasmodic, insecticidal, anti-spermatogenic, antitumor, hypercholesteric, hypoglycaemic, immunomodulator5-6 [7].

Medicinal use: all parts of the tree have been medicinally used for decades. It has been used in Ayurvedic medicine for more than 4000 years because of its medicinal properties. The earliest one Sanskrit herbal writing refers to the advantages of Neem's fruit seeds, resin, leaves, roots and bark. Any of them has been used in Indian Ayurvedic and Unani medicine, and is now being used in Pharmaceuticals and cosmetics manufacturing. 6 [7].

Use of Neem during COVID-19 pandemic in India:

In two ways neem was used during this period

1. Internal Use: Used in supplements

2. External Use: Various compounds of neem are used in Hand Sanitizer, Hand wash, Soaps and in cleansing agent.

THERAPEUTIC POTENTIAL

Antibacterial compounds: recent studies on antibacterial behaviour in the mouth, Specifically in gum disease and cavities, as well as in the treatment of sexually transmitted infections and for contraception to the vagina 6 [7, 8].

Antifungal Properties: current research has shown its antifungal properties which control fungi this can cause athlete's foot, ringworm, and Candida, an organism that causes yeast infections. and it's thrush 6 [7,9].

Anti-inflammatory: Nimbidin, a part of Neem, has been shown to have potent anti-inflammatory properties and the function of antiarthritis. Nimbin suppresses macrophage roles and neutrophils implicated in inflammation of the body. 6 [7,10].

Antioxidant Compounds: The process through which free radicals are created, is a normal function of the body, but the resulting molecules, are unstable and may damage other cells. Disorders, including cardiovascular disease, eye health, cataracts and macular degeneration, age-related neurodegeneration (declination of brain cells and nervous system) and even cancer, are caused by high levels of free radicals. Neem protects against chemically induced carcinogens and liver damage by increasing antioxidant levels. [6,7,11].

Antiviral Compounds in Neem: Neem inhibits the growth of Dengue, a hemorrhagic virus Ebola-related fever interferes with the reproduction of the coxsackie B virus, one of the group of enteroviruses that is second only to the common cold as the most infectious viral agents in humans. 6 [7,12].

Cancer: The efficacy of Neem in inducing apoptosis or boosting the body's immune system to protect it from damage. Neem or its isolated compounds have shown impressive action against a wide range of human cancer cells, including the colon, stomach, lung, liver, skin, oral, prostate, and breast. 6 [7,13].

Potential Contraceptive Properties of Neem: Consumption of Neem as either a pre-or post-coital contraceptive to avoid the spread of sperm cells at concentrations as low as around 0.05 to 1%. Purified Neem extracts contained immunomodulators that activate cells and macrophages that end the pregnancy. Fertility was restored after one or two periods without any significant effect on potential birth. 6 [14].

Immuno stimulatory Compound: Immuno stimulating properties of neem is the most important benefit. It boosts both the lymphocytic and cell-mediated systems, including "Killer T" cells which can destroy microbes, viruses and cancer cells by injecting toxic chemicals into the invaders. 6 [7,15].

Liver functions: It helps protect the liver from damage, which in turn helps to cleanse the liver. Blood. Neem leaf minimizes chemically induced liver damage by stabilizing levels of serum marker enzymes and boosting levels of antioxidants, such as those found in vitamins C and E and in natural carotenoids, which neutralize free radicals and prevent damage. 6 [7].

Neuroprotective Effect: The anti-oxidants found in neem help to prevent brain damage. He suffered a stroke by enhancing lipid peroxidation in the brain, and by elevating ascorbic acid in the brain tissue. 6 [7].

Oral Diseases and Dental Care: Another of the uses of neem has been to chew the sticks. It is still in use as an oral care commodity in rural parts of India. Neem twigs have been used in toothbrushes for decades, and they are also found to be effective in reducing plaque and gingivitis. Using neem twigs is an excellent step towards avoiding oral diseases such as bad breath, tooth decay, bleeding gums and sore gums. 6 [7,16].

Stress: Neem extracts appear to have a mild sedative effect. The medication has significant side effects at high doses, about 400 milligrams to 800 milligrams of body weight per kilograms of weight. This exercise will also relieve nervousness and tension. 6 [7].

Ulcers: It decreases Gastric acid secretion as well as volume of gastric secretion and pepsin production by 77 percent, due to its anti-inflammatory components, gastric damage is prevented decreased. 6 [7].

Arthritis: Neem has a long history of relieving joint pain. Neem not only helps to minimize inflammation but also to suppress pain. It is useful in rheumatism as well. 6 [7].

Heart Disease: Significant causes of a heart attack include blood clots, high cholesterol, arrhythmia. Hypertension is a heart condition. Its medicinal leaf extracts have resulted in decreased blood clotting, lowered blood pressure, lowered cholesterol, lowered heart rate, and stopped irregular heartbeat. 6 [7].

Malaria: Malaria is very prevalent in India and the tropics. Neem is effective in preventing the normal development of the malaria organism. Even though it may be effective against parasites that carry malaria, at present, it has not been shown to avoid malaria once it reaches the body. Burnt dried margosa leaves are used as a mosquito repellent. 6 [7].

Skin Diseases: Neem oil is useful in controlling harmful fungi, parasites, and viruses. LUCC has helped people tackle a range of healthcare issues. they begin to evolve. Psoriasis can be successfully treated by using neem oil. 6 [7].

Vitiligo: Vitiligo is considered to be an autoimmune disease that causes skin patches to lose colour. The dose is four grams of Neem leaves three times a day, preferably taken before each meal. Neem oil used in the affected areas will help to reverse discolouration. 6 [7].

AIDS: Some of the research indicated is that Neem may help in the search for prevention or a cure for AIDS. AIDS may be treated by ingesting Neem leaf extracts or the whole leaf or by drinking Neem tea. Mbah studied on in HIV/AIDS patients, 12 weeks of oral administration of acetone water neem leaf extract (IRAB) had a major in vivo impact on CD4 cells (which decreases HIV) without any adverse effects in patients. Of the 60 patients that finished the procedure, 50 were completely laboratory-compliant. The mean CD4 cell count rose by 159 per cent in 50 patients, which is a substantial increase; the number of HIV/AIDS pathologies decreased from 120 baselines to 5; and significant changes in body weight (12 per cent), haemoglobin concentration (24 per cent) and lymphocyte differential count were reported (24 percent). 6 [17].

RISK FACTORS

Given its durable characteristics, neem deserves to be used with respect. Indiscriminate use of its extracts, particularly when taken in overdoses, can cause unpleasant side effects. There are some people. Overly allergic to neem products that may cause itching, swelling of the mouth and throat, wheezing and occasionally trouble to breathe [18]. The use of neem or its derivatives can also be a cause for damage to the liver and kidneys that may result in jaundice and poor to no development of urine. While neem has some hemato-stimulatory effect as seen in mice, it may also have the destruction of red blood cells. Inappropriate use of neem can induce neurotoxicity. One of the main questions regarding its use is its ability to interact with the natural reproductive system that causes infertility [19]. DNA methylation is a major epigenetic regulatory mechanism. Statistically negligible reduction methylated deoxycytidine has been found in the infertile male neem community relative to untreated male neem group. Neem has been in use since the beginning of humanity; however, no serious adverse effects have been recorded. Since ancient times, thus, the neem tree has been kept in bay from daily dwelling sites [20].







POSSIBLE USE OF NEEM FOR COVID-19 TREATMENT

According to WHO, COVID-19 is the disease caused by a new coronavirus called SARS-CoV-2. The most common symptoms of COVID-19 are ,Fever, Dry cough, Fatigue, other symptoms that are less common and may affect some patients include: Loss of taste or smell, Nasal congestion, Conjunctivitis (also known as red eyes),Sore throat, Headache, Muscle or joint pain, Different types of skin rash, Nausea or vomiting, Diarrhea, Chills or dizziness. Symptoms of severe COVID-19 disease include: Shortness of breath, Loss of appetite, Confusion, Persistent pain or pressure in the chest, High temperature (above 38 °C). Other less common symptoms are: Irritability, Confusion, Reduced consciousness (sometimes associated with seizures), Anxiety, Depression, Sleep disorders, more severe and rare neurological complications such as strokes, brain inflammation, delirium and nerve damage [21]. Xu *et al.*, 2020 reported common clinical symptoms for COVID-19 infected patients are Fever,

cough, respiratory symptoms, and shortness of breath [22]. Neem leaf crude extract is a widely used ayurvedic medicine to treat normal fever and malarial fever (Al-Hashemi and Hossain ,2016; Sujarwo *et al.*, 2016) [23,24]. Crude aqueous extract of neem leaves was also recorded to be effective against Dengue fever-related clinical symptoms in suckling mice model. The Neem leaves extract was observed to have inhibitory potential on Dengue virus type-2 replication under both *in vivo* and *in vitro* conditions [25]. Diarrhoea is another commonly observed clinical symptom for COVID-19 Infected patients. Neem leaves are used to treat Gastrointestinal disorder like diarrhea in different parts of India as a traditional practice [26]. Additionally, Neem leaf, flower, and stem bark extracts were observed to have strong antioxidant potential [27]. The extract of dried Neem leaves was recorded to enhance antioxidants in the rat model. Neem bark extract was observed to have antioxidant potential by directly scavenging the hydroxyl radical (OH) and preventing the hydroxyl radical-mediated oxidative damage in the rat model [28]. Most importantly, Neem leaves extract was reported to induce a cell-mediated and humoral immune response in albino mice model [29]

Neem leaf glycoprotein is efficient in maintaining normal immune homeostasis through type 1 response regulation in mice [30]. Aqueous preparation of Neem leaf was also found to strengthen the type 1 immune response against an antigen in mice and rats diagnosed with breast tumor [31]. Studies indicated that Neem leaves in broiler feed may be useful against the new castle and infectious bursal disease viruses for the development of antibodies [32]. Neem leaf extract was also found to improve immunity in patients with HIV/AIDS by increasing CD4+ cell levels [17]. Neem leaf extract was also reported to act as an adjuvant in mice model to increase the immunogenicity of poorly immunogenic surface antigen vaccine. Neem leaf glycoprotein was observed to induce maturation of dendritic cells and to present macrophage-mediated antigen in mice model [33,34]. There is no experimental evidence available to correlate the therapeutic ability of Neem to treat patients with COVID-19. Due to its multidimensional therapeutic ability, it can be hypothesized that, in addition to modern medicinal methods, Neem may be an important ayurvedic medicine for the prevention and treatment of COVID-19. To develop the standard formulation of Neem or Neem derived components for the treatment or prevention of highly infectious COVID-19, a series of experimental databases and translational research is needed [35]. In March 2020, false claims were circulated on social media in various Southeast Asian countries, supporting the use of neem leaves to treat COVID-19. The Malaysian Ministry of Health summarized myths related to using the leaves to treat COVID-19 and warned of health risks from over-consumption of the leaves. There is no evidence for the effectiveness of neem leaves in the treatment of COVID-19 [36].

Table 2: Uses of Neem Plant Parts [17, 22-31]

Parts	Medicinal Uses	Pictures
Twigs	Used to scrub teeth, it kills germs, keeps up the soluble dimensions in salivation, keeps microscopic organisms under control, treats swollen gums and gives more white teeth (Rudra <i>et.al</i> ,2019). Modern tooth care products (Prashant <i>et.al</i> ,2007). Relieves cough, asthma, piles, intestinal worms, spermicidal (Biswas <i>et. al</i> , 2002).	
Fruits	Used as laxative, anti-haemorrhoid and anthelmintic (vermifuge) in nature (Rudra <i>et.al</i> ,2019). Relieves piles, intestinal worms, urinary disorder, epistaxis, eye problem, diabetes, wounds (Biswas <i>et. al</i> , 2002).	
Leaves	Treatment for acne (Bhowmik <i>et.al</i> ,2010), infusion of leaves can also be used in the treatment of sore throats (Biswas <i>et. al</i> , 2002), Infusions are also used to alleviate malaria attacks, intestinal complaints, treat dental, headache, stimulating the appetite, heartburn and as insects repellent, used as a diuretic and for diabetes, also other febrile illnesses as well as to treat numerous skin diseases (Sujarwo <i>et.al</i> ,2016). Eye problem, intestinal worms, anorexia, and skin problem (Biswas <i>et. al</i> , 2002).	
Seeds, roots and bark	used to cure different ailments, such as stomach ulcers, jaundice and to overcome a variety of infectious and parasitic diseases, ranging from leprosy, chicken pox, and malaria (Rudra <i>et.al</i> ,2019).	
Neem Oil	Aqueous extracts from seeds to treat head lice, It is applied in the treatment of such skin complaints as furuncles and eczema, as well as to relieve intestinal worm infections (Forster and Moser, 2000). Used in beautifying agents and other excellent items: cleansers, hair oil, hand wash, Face wash, creams, cleanser and so on (Rudra <i>et.al</i> ,2019); Intestinal worms (Biswas <i>et. al</i> , 2002).	
Flowers	Neem blooms can be utilized to treat anorexia, nausea, belching and intestinal worms (Rudra <i>et.al</i> ,2019). Bile suppression and elimination of intestinal worms (Biswas <i>et. al</i> , 2002).	

Bark Analgesic, alternative and curative fever (Biswas *et. al*, 2002).



Gum Effective against skin diseases like ring worms, scabies, wounds, ulcers etc (Biswas *et. al*, 2002).



CONCLUSIONS

In recent years, interest in herbal remedies has been revived due to fewer adverse effects and efficacy. Among these neems, there is a rich supply of various compounds with different medicinal properties. The use of the biological and therapeutic properties of neem should be initiated in the light of these advantages of the drug discovery programme. The knowledge gathered above concerning the use of *Azadirachta indica* in the world is consistent with the available literature. Recent years, the ethnobotanical and traditional uses of natural compounds, particularly of plant origin, have received much interest as they are well tested for their potency and are widely considered to be safe for human use. It is the best classical approach to the search for new molecules for the treatment of different diseases. A detailed screening of the available literature on *Azadirachta* suggested that it is a common remedy for the treatment of diseases among different ethnic groups, Unani, Ayurvedic and traditional practitioners. Researchers are investigating the medicinal value of this herb, as it has more therapeutic properties that are not established. In modern days, special focus should be put on the prevention of both human and animal diseases using non-toxic herbal products. While some neem herbal products have been prepared, there is still a lot of scope for better use of this wonderful plant. Current time COVID 19 pandemic its use in sanitisers, handwash but *Azadirachta indica* pharmacognosy potential does not use as their beneficial properties. Pharma industries need to study the pharmacodynamic and pharmacokinetic action of their phytochemical.

CONFLICT OF INTEREST

The author states that there is no conflict of interest regarding the review, research article discussed in the manuscript.

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