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Review Article

## Reassessing the Restorative Prospectives of the King of Spices Black Pepper

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### ABSTRACT

Since ages, spices have been a crucial portion of human diets and trade. The bioactive principles in attendance are of noteworthy merit due to their advantageous probable against an array of disorders. Black pepper, amid piperine as its foremost element, holds affluent phytochemistry and also incorporates a number other important compounds like alkaloids, volatile oils and oleoresins. *Piper nigrum* is an imperative welfare spice owed to its anti-carcinogenic, antimicrobial, antioxidant apparent and gastro-defensive workings. Piperine also show evidence of speckled pharmacological characteristics like antidepressant, anti-inflammatory, immunomodulatory, anticonvulsant, antihypertensive, antitumor, anti-tussive, pain reducing, antidiarrheal, antispasmodic, and cholesterol worsening. Piperine augments bioavailability of quite a few drugs and nutrients by restraining a variety of metabolising enzymes. This review is aimed to provide restructured information in recent progression of pharmacognosy, chemistry and pharmacological behavior of this miraculous King of Spices.

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### INTRODUCTION

Black Pepper is one of the most recurrently used spices and nominated as the “King of Spices” in the midst of an assortment of spices. This spice has been a connected part of human diets. Black pepper is used as restorative agent, an additive, and in perfumery. Complete peppercorn of *Piper nigrum* or its vigorous components are being used in different types of foods and as medicine. Black pepper is omnipresent in many tropical regions like Vietnam, Indonesia, Brazil and India. Black pepper is a blossoming trailing plant included in the family Piperaceae, cultivated for its fruit, which is characteristically dehydrated by drying and utilized as a zest and seasoning, renowned as a peppercorn. Black Pepper has conventionally been used in Ayurvedic and Unani System of medications.<sup>1</sup> Black pepper is used not only in human dietaries but also for a variety of other functions such as remedial, as a stabilizer, and in cosmetics. Many profitable pharmacological scope of black pepper and its foremost vibrant principle piperine have been put forward in modern decades. When used with foods, piperine, constructively stimulates the digestive enzymes of pancreas, augments the digestive competence and drastically diminishes the gastrointestinal food transit instance. Piperine has been verified in different in vitro researches to safeguard against oxidative damage by slaking free radicals

and reactive oxygen groups. Piperine treatment has also been indicated to lesser lipid peroxidation in vivo and helpfully manipulates cellular thiol status, antioxidant molecules and enzymes in a number of investigational environments of oxidative strain. Piperine's bioavailability improving property is also to a degree ascribed to amplified absorption as an conclusion of its produce on the ultrastructure of intestinal brush boundary.<sup>2</sup> Piperine, the most important alkaloid present in *Piper nigrum*, is responsible for the black pepper's discrete sharp quality. Piperine has loads of pharmacological possessions and several wellbeing advantages, particularly against chronic syndromes, such as lessening of insulin-resistance, anti-inflammatory potential, and improvement of hepatic steatosis.<sup>3</sup> Black pepper, with piperine as an dynamic component, embraces affluent phytochemistry that also comprises volatile oil, oleoresins, and alkaloids. More lately, cell-culture experiments and animal modeling forecasted the character of black pepper against number of maladies. The free-radical forage exploit of black pepper and its dynamic ingredients might be accommodating in chemical preclusion and conniving succession of tumor enlargement. Furthermore, piperine assists in cognitive brain implementation, boost up nutrient's absorption and perk up gastrointestinal functionality.<sup>4</sup> Black pepper has an extensive

assortment of relevance. It is used as medicine, as an additive and is also used in fragrances.<sup>5</sup>

Many exceptional exploratory editorials and writings on the pharmacological prospective of *Piper nigrum* (Black Pepper) or piperine had been in print to date. It has been open to the elements that black pepper possesses noteworthy in vitro and in vivo pharmacological prospective for the supervision of assorted ailments and syndromes and is found to be undisruptive.

## PHARMACOGNOSTIC CONSIDERATIONS OF BLACK PEPPER

*Piper nigrum* is an affiliate of family Piperaceae and is firstly inhabitant to India. The plant is well known for its healing properties. It is the most recurrently used seasoning, thus also called "the King of Spices". Different types of black peppers are obtainable having dissimilar colors. The majority regularly known peppers are black and white peppers.<sup>6</sup>

*Piper nigrum* desires warm and humid spaces for growth. The plant exists in a wide range of sundry environment varying from tall elevations to assorted soil and climatic setting. It is abundant in all the tropics as well as subtropics of the planet. The geographic allotment of black pepper is prejudiced by the bare minimum temperature of the wintry month and the wettest month's rainfall. The physiological actions in the wettest periods are at their utmost. During the rainfall episodes, the blossoming occurs, fills grains and matures. Black pepper requires a plenty sum of rainfall and dampness. The ideal setting for the expansion and gardening are the warm and clammy ambiances. Black pepper productively breeds amid 20 degrees north and south latitudes. The temperature flanked by 10°C to 40°C is most advantageous for its growth.<sup>7</sup> The taxonomical classification<sup>8</sup> of black pepper is being depicted in **Table 1**.

**Table 1: Taxonomical Classification of *Piper nigrum* (Black Pepper)**

Kingdom	Plantae
Division	Manoliophyta
Class	Magnoliopsida
Order	Piperales
Family	Piperaceae
Genus	Piper
Species	nigrum

The plant can accomplish up to 50–60 cm in elevation and is characterized by its simple, alternating leaves, with a few atypical cases of reverse or verticillate leaves. It is a perpetual creeping plant and climber that requires sustaining trellises to grow similar to as escalation uniqueness as that of beetle plant. The pepper plant initiates producing tiny round berries subsequent to about three to four years of planting. Precisely, the pepper berry is a drupe, measuring about 5–6 mm in diameter, enfolding a sole huge seed at its interior. The most regularly utilized fraction of the plant is the scented fruit. Fascinatingly, white, green, and black peppers are harvest of the black pepper fruits at dissimilar full-grown phases. Black pepper carries a mightier essence in contrasting to white pepper whereas green pepper is characterized by its unsullied and verdant scent. The piperine alkaloid is accountable for the sharp savor of

black pepper.<sup>9</sup> Black pepper is the dried up green berries and it provides peppercorn. Peppercorn is desiccated fruit which has not reached full ripening step and it is main part which is communicated and exploited as spice and seasoning. In general lingo peppercorn is referred as black pepper. Peppercorn is the principally consumable section of pepper plant. Black pepper is just about full-grown absolute berry that is desiccated up and alienated from their stalks. It is an angiosperms and a climbing type flowering vine.<sup>8</sup> The Western Ghats woodlands of India are believed as a crucial center for gardening of black pepper.<sup>10</sup> The Malabar coast is the foundation of black pepper harvest in India. It is supposed that black pepper was primarily reclaimed in this region many centuries previously. The farming of pepper was the next introduced to other countries in Asia and south eastern Asia. India is the leader in the annual production of black pepper in terms of tonnage

## CHEMICAL CONSTITUENTS

A combination of many compounds is particularly responsible for the tint, scent and odor of black pepper. It contains lignans, alkaloids, flavonoids, aromatic compounds and amides.<sup>11</sup> It also includes essential oil up to 3.5% and this oil composes of sabinene, pinene, phellandrene, linalool and limonene. Additionally it consists of piperine which is a weak basic substance with chavicine which is an isomer of piperine. Piperine and chavicine are not entirely onscientious for the aroma of the black pepper but piperine communicates strong flavor to the black pepper. *Piper nigrum* contains a biologically dynamic phyto element, piperine that illustrate signs of many physiological and pharmacological characteristics including antioxidant, anti-inflammatory, anti-obesity, antitumor, anti-apoptotic, antipyretic, antifungal, anti-depressant, anti-infective and carminative behaviors. Piperine also augments the bioavailability of different natural compounds as well as drugs. Piperine stalls free radicals and reactive oxygen species with restrain of lipid peroxidation thanks to their flavonoids and phenolic contents.<sup>12,13</sup>

The chemical arrangement of piperine has the structural formula of C<sub>17</sub>H<sub>19</sub>NO<sub>3</sub> and the IUPAC name 1-(5-[1, 3-benzodioxol5-yl]-1-oxo-2, 4-pentadienyl). It is also acknowledged as piperoylpiperidine. This has been established to be a very weak base that hydrolyzes to piperidine and piperic acid.<sup>14, 15</sup> 1-Piperoylpiperidine survives as 4 isomeric structures: piperine (trans-trans isomer), isochavicine (trans-cis isomer), chavicine (cis-cis isomer), and isopiperine (cis-trans isomer). Nevertheless, the three geometric isomers of piperine incorporate about no sharpness.<sup>16</sup> Because piperine represents about 98% of the entire alkaloids in black pepper; it is well thought-out as the main provider of strong flavor and a compute of total pungency of black pepper.<sup>17, 18</sup> Piperine is somewhat soluble in water (40 mg/L at 18 °C)<sup>19</sup> and this little solubility of piperine in water and its reduced dissolution is the rate-controlling step in the absorption progression of piperine. The pharmaceutical proceedings of piperine are somewhat restricted due to its lesser aqueous solubility and because use of it at very high concentrations can be noxious for reproductive and central nervous systems.<sup>20</sup> Further explorations have confirmed the incidence of additional alkaloids, including piperanine, piperettine, piperylin A, piperolein B, and pipericine, every one of acquiring some scale of spiciness in the pepper extract. Yet, the whole involvement of these alkaloids to pungency of pepper has been quite skimpy.<sup>21</sup>

The depth analysis of the nutritional value of black pepper shows the presence of a number of vitamin, minerals,

electrolytes and dietary fibres. The nutritional value per per 100 g of *piper nigrum* has been summarized in **Table 2**.

**Table 2:** Nutritional value per per 100 g of *piper nigrum* (Source: USDA National Nutrient data base)<sup>22</sup>

Principle	Nutritional Value
Energy	255 Kcal
Carbohydrates	64.81 g
Protein	10.95 g
Total Fat	3.26 g
Cholesterol	0 mg
Dietary Fiber	26.5 g
<b>Vitamins</b>	
Choline	11.3 mg
Folic acid	10 µg
Niacin	1.142 mg
Pyridoxine	0.340 mg
Riboflavin	0.240 mg
Thiamin	0.109 mg
Vitamin A	299 IU
Vitamin C	21 mg
Vitamin E	4.56 mg
Vitamin K	163.7 mcg
<b>Electrolytes</b>	
Sodium	44 mg
Potassium	1259 mg
<b>Minerals</b>	
Calcium	437 mg
Copper	1.127 mg
Iron	28.86 mg
Magnesium	194 mg
Manganese	5.625 mg
Phosphorus	173 mg
Zinc	1.42 mg
<b>Plant Based Nutrients</b>	
Carotene-β	156 µg
Carotene-α	0 µg
Crypto-xanthin-β	48 mcg
utein-zeaxanthin	205 mcg
Lycopene	6 mcg

Peppercorns enclose a striking list of plant derived chemical compounds that are known to have disease averting and health supporting characteristics. The valuable essential oil of black pepper also hold numerous monoterpenous hydrocarbons namely sabinene, pinene, terpenene, limonene, mercene, etc., other than piperine, which altogether furnish aromatic possessions to the pepper. Black peppercorns embrace a superior sum of minerals like potassium, zinc, manganese, iron, magnesium and calcium. These are also an excellent resource of countless imperative B-complex groups of vitamins such as Pyridoxine, riboflavin, thiamin and niacin. Peppercorns possess superior supply of

scores of anti-oxidant vitamins such as vitamin C and vitamin A. Moreover, peppers are affluent in flavonoid polyphenolic anti-oxidants like lycopene, cryptoxanthin carotenes, and zeaxanthin. These composites help the body remove harmful free radicals and helps protect from quite a lot of maladies.<sup>23</sup>

## THERAPEUTIC POTENTIALS OF BLACK PEPPER

### Traditional Uses

Years ago, traders measured black pepper the King of Spices. Designated as 'black gold'; it was one of the very initial object of business between India and Europe. *Piper nigrum* has found recognition in primordial traditional medicines all over the universe for thousands of years owing to its high concentration of compelling, favorable plant compounds.<sup>4,5</sup> In traditional Ayurvedic system, pepper has been claimed to cure discontinuous fevers, to support the secretion of bile and has been recommended for neurological, dyspepsia, flatulence, constipation and hemorrhoids. The pepper plant has been widely used in traditional Chinese medication to treat epilepsy and in incidences of treating respiratory and gastric melanomas. It has also been used as anti-emetic tranquilizing, in food poisoning as well as beneficial in curing cholera, dysentery and diarrhea. In conventional Middle Eastern medicine system, black pepper has been recognized as a nerve stimulant. The folk remedies of Thailand has used the root of the plant to take care of chills, headache, adenitis, abdominal tumors, abdominal fullness, cancer, cholera, colic, kidney stone, asthma and many other symptoms. Moreover Ayurvedic also recognizes black pepper helpful in treatment of rheumatic pain, as expectorant in cough and colds and bronchitis, in different forms of intestinal and venereal diseases. The essential oils of black pepper has been widely recommended in Ayurveda in conditions of skin inflammations, toothache, congestion inside the nose, sinusitis. In western medicines black pepper has been recognized as beneficial in incidences poor digestion and winds and in a group of symptoms including upper abdominal pain. Conventionally black pepper and its prime alkaloid piperine has been utilized in the relief of a number of diverse symptoms like strep throats, migraine pains, analgesic, antipyretic, loss of appetite and also as diuretic, antiseptics and in reduction of blood sugar level. Ayurveda, Yunani, Siddha and almost all traditional forms of remedies in India has accredited pepper and piperine containing dosage forms for the management of aches and sickness of gullet. Later on it has been published that this can also be used as an anti-periodic in malarial fever. There have been instances where black pepper powder when applied externally has shown redness on skin proving to be a rubefacient in skin ailments and in hair loss.<sup>21, 24-28</sup>

Black pepper is such a condiment which has been providing innate nutritional and medicinal profit apart from its culinary relevance since years. As scientific pharmacognostic screening has evolved, the utility of pepper in pharmaceutical arena, cosmetics, and food industries as well as scientific research has been escalating.

### Anti-Cancer prospects of Black Pepper

Researchers have hypothesized that piperine, the most dynamic compound in black pepper, comprise cancer-battling properties.<sup>29, 30</sup> Black pepper counteracts cancer development unswervingly. Pepper averts chemical carcinogenesis by stimulating the xenobiotic biotransformation enzymes. Piperine hampers some of the inflammatory prone cytokines that are created by tumor cells. In doing so it interferes with the signaling mechanisms between cancer cells, thereby reducing the chances of tumor



progression. Animal researches revealed that piperine halts the replication of colon and prostate cancer cells and has even encouraged cancer cell demise. Piperine from black pepper has been showing effective in enhancing the usefulness of traditional treatment for triple-negative breast malignancy as well.<sup>31-34,30</sup> The antioxidant actions of piperine and associated unsaturated amides cooperate a preventive role in carcinogenesis. Piperine slows up the angiogenic progression which is a trait in cancer evolution *in vitro* and *ex vivo* and also has been exposed to exhibit inhibition of breast cancer cell-induced *in vivo* angiogenesis.<sup>35</sup> Black Pepper and its significant constituents has also shown promising results in repealing multidrug resistance in sarcoma cells which impedes with cancer managements mostly.<sup>36, 37</sup> Piperine is non-genotoxic and establish to acquire anti-mutagenic and anti-tumor influences.<sup>5</sup> Abundant studies have accounted for discerning cytotoxic action of piperine on cancerous cells in contrast with healthy cells and these preclinical datas are at present being utilized in intend of clinical trials with piperine.

### Black Pepper and its antioxidant property

Studies have confirmed that Black pepper can be used as an easily handy source of natural antioxidants. Piperine in attendance in black pepper is a provider of effectual antioxidants.<sup>38</sup> Rodent studies have experienced that black pepper and piperine accompaniments may perhaps trim down free radical spoil.<sup>39</sup> Diet soaring in antioxidants may help avoid the detrimental effects of free radicals, which has been correlated with cancer, heart ailments, impulsive aging and a number of different disorders.<sup>4</sup> Piperine has been proved to minimize oxidative stress caused by can reduce high-fat diet induced oxidative stress to the cells.<sup>40</sup> Black pepper fundamentally sustains and boosts the levels and worth of important antioxidant compounds. It encloses quite a lot of powerful antioxidants and is accordingly one of the major imperative spices for avoiding and restraining oxidative anxiety. In addition to their through antioxidant actions, several of these compounds work obliquely by enhancing the achievement of other antioxidants.<sup>8</sup> Piperine holds back reactive oxygen species as well as lipid peroxidation owing to their phenolic and flavonoids content. The antioxidant capability of black pepper was projected through the determination of superoxide dismutase, glutathione peroxidase, catalase, together with quantification of reduced glutathione volume and the amount of protein carbonyl and malondialdehyde limits in the hippocampus.<sup>12</sup>

Antioxidants are also extensively utilized to postpone worsening of oxidizable goods such as food, cosmetics and pharmaceuticals as a natural antioxidant preservative. Oxidation is the primary basis for quality worsening during dispensation and storage of these goods, particularly foods. The essential oil in Black Pepper is the abode of antioxidant and antimicrobial terpenoids like limonene,  $\alpha$  and  $\beta$ -pinene,  $\delta^3$ -carene and  $\alpha$ -terpinene-4-ol, *p*-cymene along with most important alkaloid like piperine and its derivatives. Many studies have talked about the beneficiary effects of black pepper in food preservation purposes. Some researchers have even postulated that pepper oil had more or less the same antioxidant activity throughout the experiment as compared with marketed synthetic antioxidants like Butylated Hydroxy Anisole and Butylated Hydroxy Toluene.<sup>41-45</sup>

### Anti-inflammatory potential of Black Pepper

Inflammation is multifaceted usual rejoinder of vascular tissues to detrimental stimuli, such as pathogens, dented cells, or irritations. Inflammation can be considered as a

defense machinery of living creatures to various stimuli involving toxic compounds, and many environmental stress factors as well. Chronic inflammation may be a fundamental factor in many conditions, such as arthritis, heart disease, diabetes, and cancer. Several laboratory studies suggest that piperine; the key active composite in black pepper may efficiently brawl inflammation. Treatment with piperine in animals has shown results in less joint swelling and fewer blood markers with inflammation due to arthritis. Piperine has been shown restraining inflammation in the airways caused by asthma and recurring allergies. Piperine has illustrated a noteworthy prohibition of increase in edema intensity in a carragenin provoked test and has acted extensively on before time sharp changes in inflammatory development.<sup>46-52</sup>

### Immunomodulatory Potentials of Black Pepper

Black pepper exhibits immunity intonation effect on human body. It is competent of boosting and sustaining the quantity and the effectiveness of white cells and lends a hand to raise a powerful resistance against invading microbes and sarcoma cells within the body. In an important study, Black pepper aqueous extracts appreciably improved splenocyte propagation in a measured quantity-dependent, synergistic manner. Enzyme-linked immunosorbent assay researches have revealed that black pepper significantly augment and repress correspondingly, T helper (Th) 1 cytokine discharge by splenocytes. The nitric oxide production by macrophages is significantly amplified by black pepper hence notifying itself as a natural agent that can promote the maintenance of a healthy immune system as nitric oxide being an intercellular envoy that has been renowned as one of the most resourceful players in the immune system. *In vitro* studies with piperine have concluded that it reduces proliferative response encouraged by lipopolysaccharide and immunoglobulin IgM antibody. Piperine can even account for inhibition of IgM antibody discharge and diminished expression of cluster of differentiation.<sup>53-55</sup>

Black Pepper is a colon-gracious spice, which also defends the intestinal tract against bacterial growth. Piperine helps to kindle the body into transferring nutrients from the gastrointestinal tract and into the bloodstream, means pepper enables us to process more goodness from the food that we eat. Thus Black Pepper possesses anti-inflammatory, antioxidant and antibacterial actions, but also immune system-enhancing benefits.

### Black Pepper as Bioavailability Improver

Piperine in pepper increases the availability of valuable phyto-chemicals present in food items in biological systems and can enhance the action of biochemically energetic compounds enclosed in it. It encourages the speedy absorption of certain chemicals from the gastrointestinal tract, defending them from being wrecked down by compounds in the intestinal lumen and by enzymes that happen in the cells lining of intestines. Once the composites have got into the blood torrent, piperine affords fortification against oxidative scratch with the assist of liver enzymes. In this way black pepper enables us to gather most advantageous benefits from the natural medicinal compounds found in other dietetic spices. Black pepper's bioavailability augmenting characters makes it as one of the most essential spices.

Research on piperine from Black pepper given as oral supplementation has shown increase in plasma levels of coenzyme Q10.<sup>56</sup> Serum level of  $\beta$ -Carotene has been found to be increased by piperine, thus to overcome vitamin deficiency piperine enhanced  $\beta$ -Carotene uptake can be

beneficial for maintenance of health.<sup>57</sup> Also, the serum concentration, absorption, bioavailability of another important anticancer phyto compound curcumin have been found to be influenced by piperine.<sup>58</sup> *Piper nigrum* promotes the gastrointestinal absorption and liver metabolism of vasicine and sparteine causing an increase in their bioavailability.<sup>59</sup> Black pepper is expanding bigger consideration as a bioavailability enhancer in the formulations of several drugs. The pharmacokinetic profile of a number of synthetic drugs like omeprazole, propranolol, ampicillin, norfloxacin, ciprofloxacin, amoxicillin, isoniazid, theophylline and phenytoin has been influenced or improved by piperine.<sup>56, 60, 65</sup> Promising results have also been evident in plentiful other other pharmaceutically active chemicals like nevirapine, diclofenac, midazolam, tamoxifen, carbamazepine to name a few.<sup>66-68</sup> Piperine has also found to affect enzyme commotion and biotransformation. It has been reported to hinder enzymes significant for drug metabolism and in this fashion holding backing drug metabolism it may possibly augment the bioavailability of various compounds and hence amend the value of some useful therapeutics.<sup>69</sup> Piperine is blessed to have a speedy absorption rate through the intestinal barricade. Several findings have suggested that the alkaloid has a submissive diffusion system, a high evident permeability coefficient, and diminutive clearance duration.<sup>70</sup> Owing to its non-polar character, piperine is capable of controlling the membrane characteristics by intermingling with lipids and hydro anxious parts of the protein, which amend enzyme conformation owed to a decline in the property of membrane lipids to function as steric restrictions to enzyme proteins. Piperine causes an increase the penetration all the way through the epithelial barrier as it is able to persuade changes in membrane dynamics and permeation features, along with orientation in the permutation of proteins related to the cytoskeletal purpose which boosts the absorptive surface of the small intestine.<sup>71</sup> There are research datas showing black pepper and its key alkaloid vividly increasing the absorption of selenium, vitamin B as well.<sup>72</sup> Piperine has been performing the part of a bio-enhancer in the of some important chemotherapeutic agents like acyclovir, gatifloxacin, docetaxel. A number of patents have been related to the increase the bioavailability of nutritional compounds making high purity piperine for nutritional use.<sup>73-76</sup>

### Black Pepper and its cholesterol lowering potential

Obesity and high blood cholesterol is a universal peril associated with an amplified risk of heart disease, which is one of the foremost reasons of casualty globally.<sup>77</sup> Black pepper extract has been considered in animals for its probable to trim down cholesterol levels.<sup>26, 78</sup> It has been concluded that piperine can reduce cholesterol uptake by internalizing the cholesterol transporter proteins in high-fat diet-induced obesity in rats.<sup>79</sup> Black pepper does not contain cholesterol as one of its active chemical compound. It improves digestion procedure by facilitating quicker split down of bigger fat molecules into effortlessly digestible uncomplicated molecules and averts the buildup of fat in body.<sup>8</sup> Furthermore; piperine is alleged to heighten the absorption of dietary supplements that have potential cholesterol-lowering properties.<sup>80</sup> Genome-wide examination by means of microarray has also holds up the compelling task of piperine in gene regulation coupled with lipid metabolism.<sup>81</sup> Supplementing piperine with elevated fat diet has shown to be significantly reducing body weight, entire cholesterol, triglyceride, low and very low density lipoproteins and fat cluster with an augment in the degree of high density lipoprotein with no amend in dietary intake.<sup>82</sup>

Thus it can be postulated that black pepper possesses impending lipid diminishing and fat sinking effects, not including any alteration in the desire for food. Some researchers have commented that the dietary ingestion of black pepper diminishes the threat of artherosclerosis via hypolipidemic and antiatherogenic reactions.<sup>40</sup> In another finding, it has been pointed out that piperine decreases cholesterol uptake and improves translocation of cholesterol hauler proteins.<sup>83</sup> Further studies are being conducted to prove whether black pepper itself has noteworthy anti-obesity potentials in humans.<sup>84, 85</sup>

### Antimicrobial potency of Black Pepper

Loads of literatures confirm the antimicrobial potential of black pepper. There have been reports of inhibitory antimicrobial potential against different strains of *Pseudomonas aeruginosa*, *Candida albicans*, *Staphylococcus albus*, *S. typhi*, *E. coli*, *B. megaterium*. Antimicrobial activity of some synthetic piperine derivatives were confirmed against *A. fumigatus*, *Bacillus subtilis*, *Streptobacillus species*, *Staphylococcus aureus*, *E. coli*, *Salmonella typhi*, *Aspergillus Niger* and *A. flavus*. Piperine has indications of increasing the antimicrobial exploit of ciprofloxacin against *E. coli* and *Bacillus subtilis*. When tested against the fungal strain of *Fusarium oxysporum* piperine has scored maximum anti-fungal activity amongst some other microbial groups. Another research reports the leishmanicidal activity of ethanoilic and hexane extract of Black pepper against leishmanicidal activity against *Leishmania donovani* promastigotes and amastigotes through apoptosis. Some derivatives of piperine have also been active against *Leishmania amazonensis* and *Trypanosoma cruzi* amastigotes. These significant antimicrobial effects in extensive assortment of micro-organism imply piper nigrum as a authoritative natural antimicrobial agent. Moreover the antimicrobial potential of Black pepper makes it a choice able agent against food spoilage. Researchers have confirmed the usefulness of black pepper in microbiological preservation against *Listeria monocytogenes* in as well as against a general microbial load in food samples.<sup>86-95</sup>

### Antidiarrheal effects with Black pepper

Black pepper is also effective against some bacteria which are responsible for causing diarrhea. Research denotes the enormous potency of this condiment in managing diarrhea which is still a cause of high infant mortality rate in some parts of the globe. The incidence of carbohydrates and alkaloids in black pepper has been cited as the rationale of noteworthy dose-dependent anti-diarrheal effects. Piperine has inhibited gastric emptying of solids and liquids in rats and gastrointestinal transit in mice in a dose and time reliant behavior.<sup>96, 97</sup> An important finding has concluded that piperine show evidence of antidiarrheal and antispasmodic behavior, intervened possibly through calcium channel barricade coupled with some additional mechanisms. Piperine has been found equally beneficial in controlling castor-oil stimulated diarrhea like loperamide, a well-recognized antidiarrheal drug which also constitutes piperidine ring in its moiety just like piperine.<sup>98, 99</sup>

### Black Pepper and its gastro-protective properties

Piperine can perk up digestion and kindle the secretion from the taste buds and this stimulus is a feedback loop for digestion progression. It transmits impulses to the stomach to amplify digestive Hydrochloric acid secretion. These juices fracture down the protein in the stomach, making better capability for auxiliary digestion in the duodenum. Black pepper constituents encourage bile acid production which is extremely crucial for fat absorption and digestion by the

liver and its secretion into bile.<sup>100</sup> It has already been established previously that piperine can boost absorption of selenium, vitamin B, beta-carotene and curcumin in the body.<sup>57, 72</sup> Piperine also has been reported to promote sweating (diaphoretic) and urination process (diuretic). This astonishing condiment supports the healthiness of the digestive tract and helps to obtain the most assistance from food matters. Different findings illustrate the hepatoprotective effect of Black pepper in both animals and humans.<sup>6</sup> A study has reported the methanolic extract of Black pepper to be beneficial in ethanol-CCl<sub>4</sub> persuaded hepatotoxicity in rat models. Black pepper has been found to decline the hepatic biomarker intensity of some of the important chemicals including bilirubin which gets amplified in hepatotoxic conditions.<sup>101</sup> In calculated doses, piperine has reported to restrain enhancement in SGPT and SGPT levels in liver and suggested that this effect depended on hepatocytes diminished sensitivity headed for tumour necrosis.<sup>102</sup> Enhanced intestinal lipase activity has been cited as one of the reasons of piperine's role in improving digestion as it is already known that lipase is an enzyme promoting breaking down of fats in food to facilitate their intestinal absorption.<sup>103</sup> Significant increase in gastric cell exfoliation, pepsin discharge with potassium loss has been observed in a study on human models with intragastrical administration of 1.5gm per meal feed of piperine.<sup>104</sup> Piperine has also been postulated to activate salivary amylase with enhanced production of the saliva, and promote gastric secretion, more over decrease gastrointestinal transport time.<sup>2</sup> Eating black pepper regularly in calculated quantities may awaken the discharge of enzymes in pancreas and intestines that help digest fat and carbohydrates.<sup>103</sup> Owing to such positive effects on stomach function, black pepper may play a constructive role for those with pitiable digestion. Dehydrated fruits of *Piper nigrum* have been recently used in gastrointestinal problems since ages.<sup>105, 106</sup>

#### **Beneficial effects of Black pepper in central nervous system**

The nitrogen bearing sharp alkaloid piperine is one of the major functionally active constituents responsible from neuropharmacological activities of *Piper nigrum*. Antidepressant, anti-anxiety, neuroprotective and anti-neuro-inflammatory properties of Black pepper extracts have been examined in multiple animal studies.<sup>107</sup> A study performed with methanolic extract of black pepper seeds suggested that it may have potent anti-neuroinflammatory effects and may be hopeful in the management of Alzheimer's disease.<sup>108</sup> Piperine has appreciably demonstrated antidepressant and anxiolytic effects by attenuation of oxidative stress in different animal models.<sup>109</sup> It has been reported piperine generates antidepressant-mimic effects through the hindrance of enzymatic activity of monoamine oxidase and escalating the intensity of monoamine neurotransmitters in animal models of behavioral depression and encouraging reports have been noticed in swim and tail suspension tests in animals with piperine treatment.<sup>110</sup> Piperine administration in corticosteroid induced depression animals has resulted in marked reduction of unhappy behaviours and the probable mechanism has been attributed to inflection of brain-derived neurotrophic factor signalling.<sup>111</sup> Diverse researches have concluded that piperine owns intense effects on neurodegenerative turmoils of the central nervous system like Parkinsonism and Alzheimer's disease.<sup>107</sup> Presently, quite a variety of piperine-loaded nanosystems like nanocapsules, solid-lipid nanoparticles; emulsions etc. are being designed for facilitated delivery of piperine to the brain for the treatment of neurodegenerative diseases like Alzheimer's, dementia and epilepsy in animal models.<sup>112-114</sup>

In certain preclinical findings, piperine has shown evidence of anticonvulsant effects probably intervened via GABA-ergic pathways. It has also been revealed that piperine demonstrates analgesic behaviour perhaps mediated through the opioid pathway.<sup>115</sup> The accurate dynamics and brain pharmacokinetics with piperine in addition to its dealings with other central nervous system medicines are still unexplored completely. The CNS beneficial effects of piperine have been expansively considered in preclinical models together with the advantageous exchanges between piperine and other allied therapeutic compounds. Human study confirmation on its central nervous system relevance is scarcely available.<sup>116</sup>

#### **Other remedial actions of Black Pepper**

The anti-arthritis prospective of piperine has been revealed in arthritis model of rat together with its analgesic and inflammation reduction performance.<sup>117</sup> Traditionally, black pepper has been utilized as an anti-periodic in malaria fever and hence it is alleged having antipyretic and anti-pain properties. Piperine has shown good fever reducing effect on typhoid vaccinated rabbits and other experimental animals as well.<sup>118</sup> Investigation in rodents recommend that the piperine in black pepper may well be innate pain alleviator. *Piper nigrum* L. acquires powerful analgesic performance besides being an anti-inflammatory agent.<sup>117, 119</sup> Piperine from black pepper may well assist in getting better the blood sugar metabolism. Several researches have established the fact of piperine and some of its derivatives having anti-diabetic potential.<sup>120, 121</sup> A research postulated that piperine averted diabetes by glucose transporter protein type 4 translocation through a hike in the intracellular calcium level and creation of reactive oxygen species.<sup>122</sup> Piperine has reported to appreciably improve allergic conditions like sneezing and redness tempted by sensitization of nerve endings generated from histamine release in rejoinder to antigen-antibody effects in animal models. There also been reports of reduction in eosinophil infiltration due to suppression of histamine and interleukin production. Thus Black pepper can be used in anti-allergic remedies as well.<sup>123, 124</sup> The powerful antitussive and bronchodilator features of Black pepper have been recognized quite a few times and several home remedies of cough includes a certain portion of black pepper.<sup>4, 25, 107</sup> Piper plants have been used in treatment of parasitic diseases since long and *piper nigrum* has particularly been beneficial against *Leishmania species*, *Trypanosoma cruzi* and *Plasmodium falciparum*, which are the causing agents for malaria fever.<sup>92, 93, 125</sup> Hence the antimalarial use of Black pepper can also be added to its credit.

The pungent piperine has indicated to have some role in fertility with marked increase in serum gonadotropin hormone levels when examined on the testis of albino mice.<sup>126</sup> There has been incidences of secretion of catecholamines from brain cortex of experimental rats post piperine infusion treatment.<sup>127</sup> The promising role of Black pepper in hypertension is intervened most likely through calcium channel blocking has been documented in a number of literatures.<sup>3, 128, 129, 130</sup> Piperine is also accounted to display anti-platelet activity mediated by different mechanisms.<sup>131, 128</sup> Piperine can also be administered to cancer patients prior to radiotherapy thanks to its defensive effect against radiation.<sup>132</sup> The protective effect of black pepper is in accordance with its antioxidant potential.<sup>43</sup> Research data have also confirmed that piperine have an effect on mood, memory and cognitive disorders.<sup>133, 134</sup> Moreover, Black peppers' role as growth encourager, thermogenic, anti-thyroid agent, insecticidal, chemo-preventive, fertility improving with antitumor and rubefacient properties has



also been identified in a number of literatures. Being rich in antioxidants, Black pepper is steadily gaining attention in the cosmetic industries particularly in hair and skin cosmetics. 135, 5, 8, 25

### Use of Black pepper in formulations

The “King of Spices” Black pepper has evolved a lot from merely enhancing the taste of foods to being one of the most important natural compound with diversified pharmacological actions. Largely human clinical studies are being focused on the bioavailability augmentation by co-administration of piperine with a variety of drugs. But the safety in terms of dose is a crucial factor as in preclinical studies, there has been evidences of mild toxicity in very high doses. Moreover, there are certain challenges like little water solubility, low absolute oral bioavailability and extensive first-pass metabolism is also considered in oral delivery of piperine. Different newer forms of dosage are now being designed for the safe and effective use of this condiment.<sup>136, 112, 113</sup> A number of patents have also been filed regarding the newer utilization of piperine in therapeutics.<sup>137, 138</sup> Further investigations particularly clinical trials in humans will establish more on the diversified use of the plant and its mechanism ways for safe and effective clinical delivery.

### CONCLUSION

Black pepper is one of the foremost spice seasoning used worldwide in diets. It is obtained as dried young berries from recurrent, evergreen woody climbers of *Piper nigrum L.* plant belonging family Piperaceae. The spice is mostly cultivated in tropical parts of India and Southeast Asia. This is a natural food additive that supply enormously to the savour and essence of foods, and have been recognised to own several therapeutic assets and hence is successfully used in the native classifications of medicine in various parts of the globe. Besides their conventional use, a multitude of advantageous physiological consequences have come front by broad animal studies and numerous human trials throughout the past era. Among these are their antioxidant and cancer fighting potential, antimicrobial, and immunomodulatory, anti-inflammatory, digestive, cholesterol lowering, digestive, antidiarrheal, antidepressant, anxiolytic, antidiabetic and bioavailability enhancing properties have been elicited vividly. At present several investigators have been using different novel formulations with pepper as the focal constituent for specific delivery to organs. Piperine has been a leading constituent of Black pepper which has shown promising biological effects in numerous in vitro and in vivo studies and in clinical trials as well. Wide ranges of promise are open for the expansion of purposeful foods and pharmaceuticals based on black pepper and for that extensive standardised and well-designed research is the utmost need. This review anticipates finding its utility in academia, systematic explore and existent industrialized application in signifying the black pepper is in reality the ‘King of Spices’.

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