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Biological role of *Piper nigrum* L. (Black pepper): A review

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ABSTRACT

Piper nigrum L. is considered the king of spices throughout the world due to its pungent principle piperine. Peppercorn of *Piper nigrum* as a whole or its active components are used in most of the food items. Different parts of *Piper nigrum* including secondary metabolites are also used as drug, preservative, insecticidal and larvicidal control agents. Biologically *Piper nigrum* is very important specie. The biological role of this specie is explained in different experiments that peppercorn and secondary metabolites of *Piper nigrum* can be used as Antiapoptotic, Antibacterial, Anti-Colon toxin, Antidepressant, Antifungal, Antidiarrhoeal, Anti-inflammatory, Antimutagenic, Anti-metastatic activity, Antioxidative, Antiriyretic, Antispasmodic, Antispermatogenic, Antitumor, Antithyroid, Ciprofloxacin potentiator, Cold extremities, Gastric ailments, Hepatoprotective, Insecticidal activity, Intermittent fever and Larvisidal activity. Other roles of this specie includes protection against diabetes induced oxidative stress; Piperine protect oxidation of various chemicals, decreased mitochondrial lipid peroxidation, inhibition of aryl hydroxylation, increased bioavailability of vaccine and sparteine, increase the bioavailability of active compounds, delayed elimination of antiepileptic drug, increased orocecal transit time, piperine influenced and activate the biomembrane to absorb variety of active agents, increased serum concentration, reducing mutational events, tumour inhibitory activity, Piperine inhibite mitochondrial oxidative phosphorylation, growth stimulatory activity and chemopreventive effect. This review based on the biological role of *Piper nigrum* can provide that the peppercorn or other parts can be used as crude drug for various diseases while the secondary metabolites such as piperine can be used for specific diseases.

1. Introduction

Piper nigrum is famous as the spices king due to its pungent quality[1]. *Piper nigrum* (*P.nigrum*) L. is a member of family Piperaceae[2-4]. The genus piper has more than 1000 species but the most well known species are *P.nigrum*, *P.longum* and *P.betle*; 51 cultivars of *p. nigrum* have been reported from the tropical and subtropical regions of India [5]. *P.nigrum* fruits are also used to produce white pepper and green pepper and are valued due the presence of piperine including its different isomers[6]. Black pepper can be used for different purposes such as human dietaries, as medicine, as preservatives, as biocontrol agents[1, 8, 9]. This plant and its active component piperine can stimulate the digestive enzymes of pancreas and intestines and also increases biliary bile acid secretion when orally administrated[7]. Some reports have been demonstrated that black pepper consumption in humans increased orocecal transit time[10-11]. Piperine prevents and minimize diarrhea produced by various oil and chemicals and also reduce intestinal fluid accumo-latin in mouse intestine[11]. The active agents of *P. nigrum* activates the epithelial cells in rat jejunum to permeates the uptake of various amino acids through the activation of membranes, enhance the production of proteins which are later used for the formation of cytoskeleton system due to surface adsorption property. This valuable specie also has the power to minimize different mutations like ethylcarbamte induced mutation in Drosophila. As compare to mutation, black pepper also reduced tumor formation in mice such as Ehrlich ascites tumour and Doltons lymphoma cells[12-14].

Other related activities included Anti-inflammatory activity, thermogenic action, growth stimulatory activity, anti-thyroid activity and chemopreventive[15]. Secondary metabolites from *P. nigrum* play defensive role against infections by microbes, insects and animals[16-17].

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Piperamides extracted from *P. nigrum* had shown insecticidal activities[18-19]. β-caryophyllene showed anesthetic activity[20]. Nerolidol is very famous secondary metabolite of *P. nigrum*, used to control mites. Another important component of pepper volatile oil is pipene, which is a famous odorants[21].

Black pepper is important for its medicinal value[22]. Medicinally black pepper can be used for digestive disorders like large intestine toxins, different gastric problems, diarrhea, and indigestion and also can be used against respiratory disorders including cold, fever, asthma [23, 24, 26]. The West African Black pepper, (*P. guineense*), important as flavorant and its different parts are used as internal medicine for curing bronchitis, gastric ulcer, rheumatism and as antiviral agent[25]. Recently, an interesting study has shown effects of piperine on mood and cognitive disorder[27]. Notwithstanding, it has been shown that enhances the bioavailability of various nutrients including vitamins; β-carotene and selenium[28]. Different field investigators isolated valuable compound from this specie including Phenolics, various derivatives of lignans, terpenes, chalcones, flavonoid, alkaloid and steroid[25]. Brachyamide B [29], Dihydropipericide[25], benzamide group[30], (2E, 4E)-N-Eicosadienoyl pereridine[31], N-trans-Feruloyltryamine,[25], Guineensine[32], pentadienoyl as piperidine, (2E, 4E)-N-isobutyldecadienamide[33], isobutyl-eicosatrienamide[34], isobutyloctadienamide[25], Piperamide[35], Piperamine[25], Piperettine[36], Pipericide[37], Piperine[3,38], Piperolein B, Trichostachine, Sarmentine, Sarmentosine,[39,25,4,40]. Only 12% plant species of Piperaceae family has been investigated for phytochemicals analysis. 592 compounds has been isolated which includes alkaloides/amides (145), lignans (47), neolignans (70), terpenes (89) and 101 noval compounds has also been extracted, 14 of which shown different biological activities[25, 41, 42, 43].

2. Biological value of *P. nigrum*

Most of the plant species including piper produced secondary metabolites which help in body metabolism and also used as defense system against various agents such as insect feeding plants and animals.[16]. Recently scientists from different biological fields screen plants for various secondary metabolites which can be used for preparation of medicines and biocontrol agents[45].

Piperaceae family has provided many past and present civilizations with a source of medicines and food spices; the secondary metabolites of different species in the genus piper have been used for various biological activities including insect repellent activities. The active compounds having insecticidal activity are the piperamides extracted from different species of piper including *Piper nigrum*[46]. Black pepper is the main spice food stuff and Piperine is a pungent alkaloid of black pepper. Two important sesquiterpens, β-caryophyllene and nerolidol, the first having anaesthetic activity[20]and second used for flavouring agent, it is also been reported that the piperine enhances the trans-dermal delivery of active drugs through skin membrane. A natural compound isolated from piper species known as nerolidol having pesticidal activity against various mites. Another active agent isolated from volatile oil of peppercorn known

Table 1

Mathew *et al*[44] reported 51 cultivars of *P. nigrum* in various districts of India.

No	Cultivar	Locality	District	No	Cultivar	Locality	District
1	Ampirian	Kulathupuzha	Kollam	27	Kanjiramkodan	Kalpetta	Wayanad
2	Angamali	Kodolippuram	Kannur	28	Kareelanchi	Kulathupuzha	Kollam
3	Arakulammundy	Pulpally	Wayanad	29	Karimkottavalli	Kalpetta	Wayanad
4	Areepadappan	Kulathupuzha	Kollam	30	Karimunda	Peruvanthanam	Idukki
5	Arivally	Kodolippuram	Kannur	31	Karimundy	Pulpally	Wayanad
6	Balankotta	Kalpetta	Wayanadu	32	Karivally	Porora	Kannur
7	Cheriyakaniyakadan	Veliyambra	Kannur	33	Kottanadan	Peringamala	Trivandrum
8	Cheriyauthiran	Naiketty	Wayanad	34	Kuruvantherivally	Kodolippuram	Kannur
9	Cherumany	Naiketty	Wayanad	35	Kuthiravaaly	Kodolippuram	Kannur
10	Chombala	Mattannoor	Kannur	36	Maniyamcode	Kalpetta	Wayanad
11	Jeerakamundy	Peermade	Idukki	37	Manjavallypadappan	Peringamala	Trivandrum
12	Kallubalancotta	Kodolippuram	Kannur	38	Menonvally	Kodolippuram	Kannur
13	Kallumany	Periya	Wayanad	39	Mundy	Aralam	Kannur
14	Kalluvally	Periya	Wayanad	40	Murithothan	Kulathupuzha	Trivandrum
15	Kalyanamandiram	Kalpetta	Wayanad	41	Narayakodi	Pathamuttom	Kottayam
16	Kaniyakadan	Kulathupuzha	Kollam	42	Neelamundi	Vandiperiyar	Idukki
17	Muttiyaramundy	Pulpally	Wayanad	43	Orumaniyan	Vallakkadavu	Idukki
18	Pala	Palode	Trivandrum	44	Peringamala	Peringamala	Trivandrum
19	Panickaruvally	Naiketty	Wayanad	45	Perumkodi	Pulpally	Wayanad
20	Panniyur-I	Palode	Trivandrum	46	Poonjarmunda	Kodolippuram	Kannur
21	Thevanmundy	Peermade	Idukki	47	Uthirankotta	Kodolipuram	Kannur
22	Thirimuriyan	Kalpetta	Wayanad	48	Vadakkan	Vandiperiyar	Idukki
23	Uthiran	Kalpetta	Wayanad	49	Valiyauthiran	Naiketty	Wayanad
24	Valiyapadappan	Kulathupuzha	Trivandrum	50	Vattamundy	Upputhara	Idukki
25	Vellamundy	Vallakkadavu	Idukki	51	Veluthauthiri	Porora	Kannur
26	Wayanadan	Chandanathod	Wayanad				

Figure 1. Adopted from internet (A) Climbing vine of *P. nigrum*; (B) Green mature berries of *P. nigrum*; (C) Black, white and green fruits of *P. nigrum*; (D) Processed peppercorn.

as pipene which is important odorants[21]. Black pepper stimulates rat gastric acid secretion and its active agent piperine decreases the secretion of small intestine activated by castor oil. This plant also increases rat pancreatic enzymes activity[47]. Black pepper is antimicrobial[48], same antimicrobial activities also reported from Piper betle, antimutagenic[12], antioxidant & radical scavenging properties[49-50], improve reflexive swallowing movement [51]. Black pepper and peppercorn are used to cure various digestive disorders, fevers, obesity and respiratory tract diseases caused by different pathogenic agents such as bacteria, viruses and fungal strains. Peppercorns extract contain such active spasmolytic compounds which block the Ca^{+2} influx and explain its traditional medicinal use in the curing various digestive disorders[52,23]. Aqueous decoction of black pepper has maximum effect against *Staphylococcus aureus*[53]; also inhibit the growth of meat spoilage bacteria [54]. Black pepper also have insecticidal activities[19], concentration of 0.2 μl of *P. nigrum* oil significant repellent of *T. castaneum*[55], also show anti-spermatogenic and infertility effect in mice[56], anti-diarrheal & antispasmodic activities of Piperine. The natural lipophilic Piperine and piperiline were isolated from *Piper nigrum*, Piperine was hydrolyzed into piperic acid which was converted into 16 amides having insecticidal activity[25,57]. The larvicidal activity of Piper nigru, was also reported, larvicidal effects of crude extracts of dried ripened fruits of pepper against *Culex quinquifasciatus* larval instars. Piperine displays antipyretic, analgesic, insecticidal, anti-inflamatory[57-58], immuno-modulatory, antitumar[14]and antidepressant activities[59], anti-apoptotic activity[60].Piperine derivatives from *P.nigrum* and *P.longum* having anti-metastatic activity[61], antithyroid activity[15], Hepatoprotective[62]and immunostimulating activity[14]. Antiplatelets, anxiolytic activities. It is anti-oxidant and its anti-apoptotic potential has also been reported[63-64]. Piperine inhibits several Cytochrome P450-mediated pathways in animals[22,65]. Piperine significantly increased plasma concentration of refampin, phenytoin, propranolol and theophylline in humans[66-68], a phytochemical potentiator of Ciprofloxacin against Stapyloccocus aureus. The dichloromethane extracts of *P. nigrum* has pesticidal activity against *C. masulatus* and S. zeamais[69]. *P. nigrum* inhibit the transcription of toxin biosynthesis genes in *Aspergillus paraiticus*[70]. Antifungal activity of this plant also reported against bean rust[71].

3. Effects of *P. nigrum* on digestion

The pungent compound of *P. nigrum* especially piperine increases the production of saliva and gastric secretions [1]. Furthermore, the ingestion of peppercorn increases the production and activation of salivary amylase[43]. The digestive enzymes production by the ingestion of *P. nigrum* probably the stimulate liver to secrete bile, which further digests food substances. Researchers[9]examined various animal models for bile secretion after the ingestion of piperine from *P. nigrum*. These workers further observed that orally administrated piperine can significantly increases bile acid secretion from liver. The effect of intake of peppercorn in food items and oral administration of active compounds of genus piper such as piperine, piperamides, piperamines and pipene on the enzymes activation of pancreas, liver and the terminal digestive enzymes of the small intestinal mucosa has been reported[7-8]. Addition of piperine to food substances as food additives increases lipase activity, pancreatic amylase activity, chymotrypsin activation and protease activity[1].

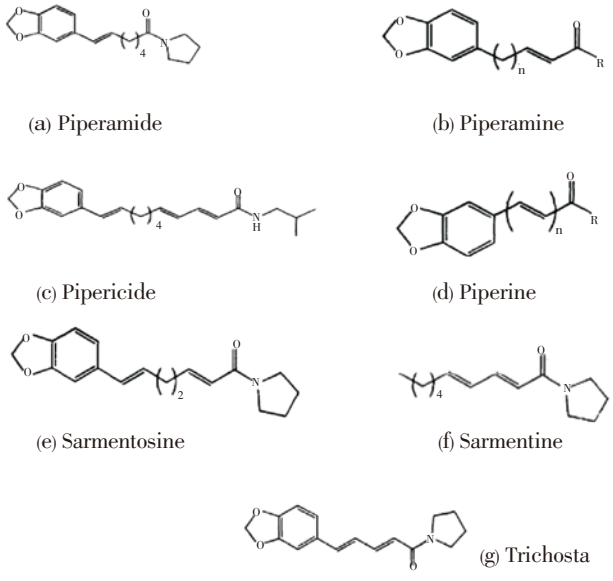

Figure 2: Some important derivatives of *P. nigrum*.

4. Antioxidant activity of *P. nigrum*

Plants are more important in human's life and fulfill his every day's needs[74]. In recent developments free radicals are involved in many diseases[40]. Different free radicals produced in the body attack on membranes causing oxidation of lipids, reduced the fluidity of biomembranes,

loss of different enzyme activities, loss of receptor activities and causing cell inactivation by damaging the proteins present in membrane[75,78]. Some Free radicals are the causing agent of cancer, first the free radicals attacks on cell DNA, the DNA causes mutational changes which finally induced cancer[76, 79]. Due to such diseases natural antioxidant are of interest for scientist to cure cellular degeneration[77, 80]. Antioxidants are such type of agents which completely stop or delay the process of oxidation. The antioxidant compounds blocked the chain reaction of oxidation. Natural and synthetic antioxidants are the two group of antioxidant but the synthetic antioxidants are carcinogenic[75, 81]. The interest in natural antioxidants have been increased considerably, especially to the antioxidant compounds present in plants which is consider non toxic and environmental friendly[75-76]. The antioxidants of plants origin are recently used as food additives[77, 82]. Reactive secondary metabolites and reactive oxygen species (ROS) produced during metabolism causes carcinogenesis and cell damage[1]. To protect themselves from reactive oxygen species such oxidative damage, plants developed a complex antioxidant system [75]. Antioxidant protection system includes enzyme like Peroxidase (POD), Catalase (CAT) Superoxide dismutase (SOD) and Ascorbate (ASC), which scavenge both radicals and their associated non-radical oxygen species. Regenerated tissues of *Piper nigrum* like callus, *in vitro* shoots, roots, *in vitro* plantlets, peppercorn and acclimated plantlets possesses antioxidant activity which is probably due to the presence of flavonoids and phenolic contents[3]. Vijayakumar *et al*[84]reported the effect of intake of *P. nigrum* on membrane lipid peroxidation, enzymic, and non-enzymic antioxidants in rats and documented that *Piper nigrum* prevent induced stress such as oxidative stress. *Piper nigrum* also prevent the intestine induced oxidative stress, inhibit lipid peroxidation, arresting different radicals such as hydroxyl and super oxides radicals, decrease induced lung carcinogenesis and inhibit human lipoxygenase[83, 84, 85, 86, 87, 92].

5. Antidiarrhoeal property *P. nigrum*

P. nigrum is important due it pungent piperine[3]. Several workers reported the antidiarrhoeal property of this plant. Interestingly in most of the developing countries local peoples, herbal practioners and herbal industries specially formulate the peppercorn for diarrhea for all ages[88]. The antidiarrhoeal activity in experimental mice has already been reported[11]. Furthermore, the piperine profile of piper species minimizes the antidiarrheal activity induced by the supplementation of various chemical activators and oil in experimental animal's model[89]. Some reports has been published on the effects of piperine in mice small intestine fluid accumulation activated by castor oil. In such induced situation piperine sequentially prevent the small intestine fluid accumulation. Furthermore, the reduction in fluid secretion and accumulation was control by capsaicin-sensitive neurons, but comparatively the capsazepine-sensitive vanilloid receptors was less effective during castor oil induced situation[88].

6. Antimutagenic and antitumor activity of *P. nigrum*

P.nigrum not only used in perfumery and food industry but also very effective against fatal diseases caused by mutations. El Hamss *et al*.[12] observed that when Drosophila melanogaster was exposed to mutation through promutagen-ethyl carbamate, in such induced situation the *P. nigrum* is effective to reduce mutational events. *P. nigrum* and its active derivatives especially peppercorn extract has been reported to inhibit tumors formation in experimental models[90]. Such reduced antitumor activity by the oral administration was also reported[3]. The alcoholic extract of peppercorn and piperine was effective in immunomodulatory, antitumor activity and Dalton's lymphoma[14]. [61]Observed that piperine are involved in antimetastatic activity, in his experiment he documented that mice models when exposed to melanoma cells (B16F-10), the active agent piperine prevent and inhibit lung metastasis and finally concluded that piperine dramatically reduced tumor nodule formation. Moreover, piperine from *P.nigrum* reduced lung cancer by modulating lipid peroxidation and through the activation of antioxidative protection enzymes[91-92].

Table 2
Different biological activities of *P. nigrum*.

S.NO	Activity	References
1	Anti-apoptotic	[63-64]
2	Antibacterial	[71]
3	Anti-Colon toxin	[52]
4	Antidepressant	[59]
5	Antifungal	[17]
6	Analgesic	[25]
7	Antidiarrhoeal	[58]
8	Anti-inflammatory	[25-58]
9	Antimutagenic	[12]
10	Anti-metastatic activity	[61]
11	Antioxidative	[3,63,64]
12	Antiriyretic	[25]
13	Immuno-modulatory	[14]
14	Antispasmodic	[58]
15	Asthma, obesity, sinus	[52]
16	Antispermatogenic	[56]
17	Antithyroid	[15]
18	Antitumor	[14]
19	Ciprofloxacin potentiator	[67,68]
20	Colic	[23]
21	Cold extremities	[23]
22	Gastric ailments	[23]
23	Hepatoprotective	[62]
24	Increase plasma	[66]
25	Increase pancreatic enzymes	[47]
26	Inhibit cytochrome	[10,65-71]
27	Inhibit transcription	[70]
28	Insecticidal activity	[46]
29	Intermittent fever	[23]
30	Larvisidal activity	[52]
31	Pesticidal activity	[69]

7. Antidepressant activity of *P. nigrum*

Table 3
Some important role of *P. nigrum* fruits and isolated piperine [1]

Different effect of *P. nigrum* and Piperine	References
Piperine inhibit ascorbate-Fe_{++}-induced lipid peroxidation	[100]
Piperine protected against oxidative stress induced carcinogenesis	[85]
Protection against diabetes induced oxidative stress	[101]
Inhibition / quenching of super oxides and hydroxyl radicals by piperine	[86]
Piperine protects Cu_{++}-induced lipid per-oxidation	[92]
Decreased mitochondrial lipid peroxidation	[84]
Dietary black pepper/piperine reduces high fat diet induced oxidative stress	[87]
Inhibition of aryl hydroxylation	[102]
Decreased UDP-glucuronic acid concentration	[65]
Inhibition of O-deethylase activities in pulmonary microsomes	[103]
Inhibition of UDP-glucose dehydrogenase and UDP- glucuronyl transferase	[104]
Increased bioavailability of vaccine and sparteine	[73]
Enhanced systemic availability of propranolol and theo-phylline	[68]
Increased serum concentration	[105]
Delayed elimination of anti-epileptic drug	[106]
Enhanced bioavailability of β-lactam antibiotics	[107]
Increased plasma levels and delayed excretion of epigallo-catechin-3-gallate	[108]
Stimulation of digestive enzymes of Pancreas by dietary piperine	[8]
Increased orocecal transit time	[109]
Black pepper increased gastric acid secretion	[110]
Piperine modulated the membrane dynamics and permea-tion characteristics,	[85]
Reducing mutational events	[12]
Tumour inhibitory activity	[13]
Anti-metastatic activity of piperine on lung metastasis	[61]
Chemopreventive effect	[91]
Thermogenic action of piperine via adrenal catecholamine secretion	[111]
Growth stimulatory activity	[112]
Anti-thyroid activity	[15]
Piperine inhibited mitochondrial oxidative phosphorylation	[113]
Piperine exerted protection against t-butyl hydroperoxide	[62]
Piperine promoted cytotoxicity induced by benzo(α)pyrene	[114]
Piperine potentiated hepatotoxicity of carbon tetrachloride in rats	[115]

Li *et al*.[93]and Song *et al*.[94]demonstrated the effect of piperine on antidepressant activity in experimental mice through chronic mild stress procedure. Dose dependant intake of piperine for 15 consecutive days reverse the chronic mild stress and changes in consumption of sucrose and also plasma corticosterone level. Furthermore, the level of brain-derived neurotrophic factor in hippocampus of chronic stressed mice was up-regulated by piperine treatment[88]. Wattanathorn *et al*.[27]also observed the antidepressant activity by the administration of piperine to Wister male rats in different doses for 28 days and finally documented that piperine possessed anti-depression like activity and cognitive enhancing effect during entire treatment duration.

8. Anti-platelet activity of *P. nigrum*

The valuable component of different piper species is piperine. Piperine is mostly responsible for various activities [1-3]. Piperine also possesses anti-platelet activity. Park *et al*[95] observed the toxic effect of piperine on aggression of platelet in experimental rabbit induced by different factors which activate platelets, by collagen and thrombin.

9. Anti inflammatory activity of *P. nigrum*

Singh and Duggal[88]in their review reported that piperine isolated from *P. nigrum* inhibits adhesion of endothelial monolayer to neutrophils and due such inhibitory activity the tumor necrosis factor-α induced expression of cell adhesion molecules was blocked i.e. intercellular adhesion molecule-1, vascular cell and E-selectin. Vijayakumar [84] also reported another blocking system that piperine blocks the phosphorylation and degradation of IκBα by attenuating tumor necrosis factor-α induced IκB kinase activity. Piperine in various concentrations, dose-dependently inhibited the collagen matrix invasion of melanoma cells (B16F-10)[61]. Singh and Duggal[88]also documented that GM-CSF, IL-6, TNF-α and IL-1β which was pro-inflammatory cytokines was dramatically reduced by the administration of piperine.

10. Antihypertensive effect of *P. nigrum*

P. nigrum are mostly administrated orally as food additives. For more specification the isolated components like piperine are administrated by different means. Piperine in dose-dependent manner when administrated

intravenously, it induced to decreased pressure in arteries in normotensive anesthetized rats[96]. Piperine, in *in vitro* study on rabbit heart causes a partial reduction of force, contraction of tissues and blood flow in coronary vessels. In rabbit aortic ring, piperine partially inhibited phenylephrine and inhibited high K^+ pre-contractions due to blockade Ca^{2+} channel. In Ca^{2+}-free medium, piperine in low doses exhibited vasoconstrictor effect[88].

11. Hepatoprotective effect of *P. nigrum*

After Silybum marianum as main hepatoprotector, *P. nigrum* also possess hepatoprotective effects in experimental animal's models and in humans. Matsuda *et al*.[97]observed that when experimental mice with D-galactosamine induced liver toxicity were exposed to dose-dependent piperine, it inhibited increase in serum GPT and GOT levels and suggested that this inhibitory effect depended on the reduced sensitivity of hepatocytes to tumor necrosis factor $-\alpha$[88].

12. Antithyroid activity of *P. nigrum*

P. nigrum and its active piperine alone can be used for a variety of diseases. But when piperine in combination with carbimazole was administrated, it has been observed that the combination dramatically reduced the lipoproteins and plasma lipids, furthermore such combination increases the high density lipoproteins level[98]. Singh and Duggal[88] also reported that piperine supplementation significantly reduced TSH and apo B, however the testosterone, apo A-I, T4 and T3 level were increased. Panda and Kar[15]administrated Swiss albino mice with piperine and recorded lowered thyroxin and triiodothyronine, serum levels of both the thyroid hormones and as well as glucose concentrations with a concomitant decrease in hepatic 5'D enzyme and glucose-6-phospatase activity.

13. *P. nigrum* as antiasthmatic

Most of the herbal practioners and old people believed that addition of powdered peppercorn to green tea reduced asthma[3-4]. Kim *et al*.[99]reported that oral administration of piperine in different proportion to mice suppressed and reduced the infiltration of eosinophil, hyper responsiveness and inflammation due the suppression of the production of histamine, interleukin- 5, immunoglobulin E and interleukin-4.

14. BioPerine from *P. nigrum* fruits

BioPerine is a standardized extract from the fruits of *Piper nigrum* L., contains 95% piperine which is very effective for both human and animals when used as food additives[116]. BioPerine can be co-administrated with herbal extracts, water-soluble vitamins, fat-soluble vitamins, antioxidants, amino acids and minerals. BioPerine has been termed a natural Thermo-nutrient and bioavailability enhancer[117]. BioPerine in small amount with beta-carotene increased two fold the blood levels of beta carotene in human[118]. BioPerine also enhanced the bioavailability of drugs. The therapeutic effectiveness of curcumin is limited due to its poor absorption from the GI tract, therefore the BioPerine significantly improved the uptake of Curcumin.

15. Cosmoperine from *P. nigrum* fruits

Cosmoperine prepared from piperine used in cosmetics, a natural bio-enhancer which improve the permeability of active compounds through skin[116]. Cosmoperine activate and stimulate the natural power of skin to absorb nutrients[119-120]. Cosmoperine isolated from piperine are non-irritant, interacts with the skin quantitatively and qualitatively in various means. Furthermore, Cosmoperine are pain relieving and causes skin reddening due to vascular engorgement as well as a slight skin tingling sensation.

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