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REVIEW ARTICLE

Piperine and Its Various Physicochemical and Biological Aspects: A Review

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Abstract: *Piper nigrum* L. is examined as the king of species worldwide by virtue of its principle piperine. In Ayurveda, since from the ancient times, it is known as “Yogvahi”. It is one of the important alkaloids of Pepper fruits (Family Piperaceae) and has been found to have numerous medicinal properties such as antioxidant, antiplatelet, anti-inflammatory, antihypertensive, hepatoprotective, antithyroid, antitumor, antiasthmatic activity and also have significant role as fertility enhancer. The present review discusses the biosynthetic pathway, extraction process, chemistry and various analytical methods of piperine. It also describes the structural modification of piperine and its various effects on biological system. The utility of piperine as a bioenhancer for certain antibacterial-antibiotics and a potent inhibitor of drug metabolism are also discussed. Thus, review provides knowledgeable erudition on the piperine which paves way for further work.

Keywords: Piperine, Bioenhancer, Biological activity, *Piper nigrum*.

1. INTRODUCTION

Piperine is an interesting compound because it is a good biomarker together with other pure bioactive components or their derivatives or with drug molecules and hence proves to be potential drug compound. Since from the ancient time, piperine the bioactive natural compound belongs to the Piperaceae family, detected in piper species such as *Piper nigrum* L. (Black Pepper) and *Piper longum* L. (Long Pepper) [1] and has been investigated its utilization in various applications. Apart from piper species, it also exists in the leaves of *Rhododendron fauriei* (Ericaceae) [2], *Vicoaindica* (Asteraceae), seeds of *Anethumsowa* (Apiaceae), *Fructus piperis* Longi [3] and bark of *Careya arborea* (Lecythydaceae) [4]. Piperine is an alkaloid with a formula $C_{17}H_{19}NO_3$ and molecular weight of 285.34 daltons. It belongs to the largest class of plant secondary metabolite termed as alkaloids. It is a solid substance, insoluble in water, and has weak basicity character, tasteless at first, but leaves a burning taste after a while. The alkaloid piperine is rationally used for the pungency of the plant [1] which belongs to the vanilloid family of compounds; *i.e.*, capsaicin, the pungent substance found commonly in hot chilli peppers. However, plants containing the alkaloid, piperine are commonly found to be used in various traditional systems of medicines for curing an array of disorders and as spices globally [1, 5]. This review presents all available information on the biosynthesis, extraction methodologies, chemical synthesis, analytical data reports and biological properties of piperine and is summarized to create an overview of piperine content.

2. BIOSYNTHESIS OF PIPERINE

Piperine belongs to the alkaloidal class of secondary metabolite whose biosynthesis is probably initiated by sequence of reactions *i.e.* condensation, decarboxylation, oxidative deamination and cyclization. The various

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investigation suggests that biosynthetic pathway enroute to piperine would involve the amino acid precursor L-lysine. The whole biosynthetic process involves two steps. Step 1 primarily occurs through condensation reaction involving N-heterocycle piperidine and thioester piperoyl- CoA, which provides the group-transfer potential required in the reaction (Fig. 1b) [6]. The N-heterocycle piperidine generates from the decarboxylation of amino acid L-lysine in the presence of pyridoxal phosphate (PLP) to cadaverine, which go through oxidative deamination directly by the enzyme diamine oxidase to yield an amino aldehyde. Then this amino aldehyde further put up cyclization to give the imine, $\Delta 1$ -piperideine, which further reduces to piperidine (Fig. 1a) and then this generated piperidine reacts with piperoyl-CoA (step 2) to give piperine [7]. However, this propose mechanistic study has not been proven yet; therefore, various enzymatic studies based on the biosynthesis of analogous compounds such as coumaroylagmatine [8, 9] and feruloyltyramine [10, 11] were carried out, which presents clear evidence that the formation of such type of acid amide linkages can be met *via* intermediate acyl-CoA derivatives.

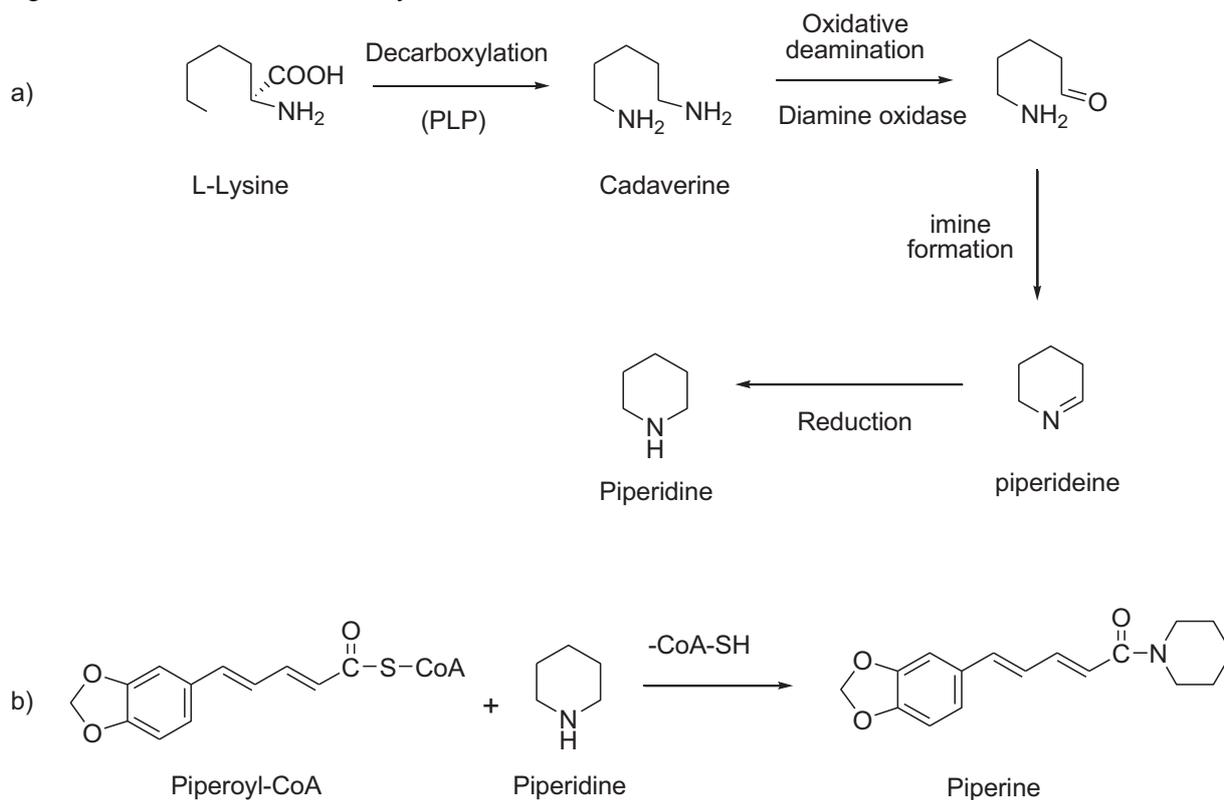


Fig. (1). (a) Biosynthesis of Piperidine from L-Lysine (b) Reaction catalysed by piperidine piperoyltransferase from *Piper nigrum*.

In case of concerning the biosynthesis of natural alkaloid piperine, the two major requirements are successfully fulfilled by the preparation of piperoyl-CoA [12] and by this discovery it was demonstrated that a new acyltransferase obtained from the shoots of *Piper nigrum* is capable to synthesize appreciable amount of piperine in the presence of piperoyl-coenzyme A and 2 piperidine and thus represent a potential enzymatic source [13]. Various studies provides information regarding the reaction rate while using different substrates and minor reaction rates are observed with bases like pyrrolidine and 3-pyrroline where as other related heterocyclic nucleus like pyridine, pyrrole, tetrahydropyran *etc.* are not accepted as good substrates.

3. EXTRACTION TECHNOLOGIES

Piperine is a pungent natural alkaloidal product and secondary metabolite extracted from the plant of the genus *Piper*. It is an obtained or isolated from the oleoresin of *P. nigrum* or *P. longum*. Various extraction methodologies were employed to isolate the piperine which depend upon the scale and as well as the purpose of the product and operation. Maceration or Soxhlet extraction of fruit powder with polar organic solvents obtains dark-brown oily substance, which on fractionation by column chromatography using hexane and diethylether (1:2) as mobile phase gives piperine and related amides [14] (Figs. 2 and 3). Pure piperine can also be obtained by supercritical fluid extraction, followed by crystallization from ethanol [3, 15]. However, Supercritical fluid extraction of Pepper generally requires high rate of

pressures and temperatures and helpful in consuming the reduce amount of solvent. In addition, the molecule gains an important position in today's discovery programme and it is being tempted by the people to be developed or isolated in its purest form by employing newer green technologies: using microwave [16] and by hydrotropic solubilisation [17], so that it can be directly used medicinal preparations without any further processing. Furthermore, piperine like compounds from Piper species have been extensively isolated, fractionated and identified by employing High performance liquid chromatography [18, 19]. It is also reported in literature that previously developed methods measures the plasma as well as tissue levels of piperine in animals [20, 21]. In recent years, piperine content can be detected upto nanogram/pictogram level using HPLC as well as HPTLC methods [22 - 24].



Fig. (2). Brief outline of obtained piperine.

4. CHEMICAL SYNTHESIS OF PIPERINE AND RELATED COMPOUNDS

Due to the most effective bioactive constituent, it received a potential greater interest in their synthesis so they can be employed as potential pharmaceuticals. Piperine exists as trans-trans isomer of 1-piperoyl piperidine. The above structure of piperine (Fig. 4) has been unambiguously confirmed by number of synthetic routes [25 - 32]. Piperine can be stereo selectively synthesized by Horner-Wadsworth-Emmons Reaction (Fig. 5). Preparation of piperine involves reaction of phosphonate ester of methyl-4-bromo-2-butenate and piperonal in the presence of sodium methoxide. This generates the phosphate carbanion which further undergoes a Wittig type reaction to form the trans alkene, methylpiperate {(E, E)-5-(3, 4-methylenedioxyphenyl)-2,4-pentadienoate}. Thus, reaction of methyl piperate with piperidine in the presence of sodium methoxide and methanol gives piperine [33]. A more recent preparation of piperine analogues is given by Schobert which utilizes intermolecular three component reaction between aldehydes (alkyl or aryl), amines (1° or 2°) and ketenylidetriphenylphosphorane (Fig. 6) [34]. Apart from this, various amide analogues of piperine were synthesized by using substituted aromatic aldehydes [35] which generally undergoes alkaline hydrolysis in presence of ethanol and provides the basic units such as piperidine, pyrrolidine or isobutyl amine and their corresponding acids such as piperic acid or piperilic acid or guineensic acid, depending on the nature of the carbon chain of the respective amide [36, 37].

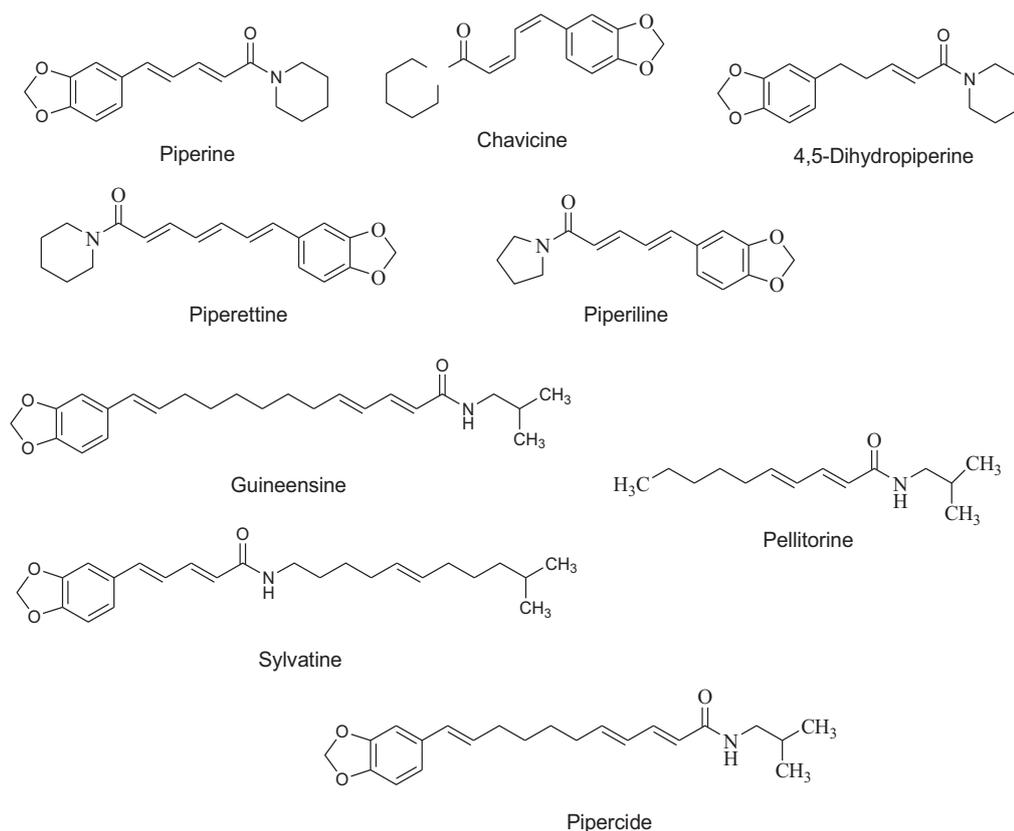


Fig. (3). Piperine-type amides from the genus *Piper*.

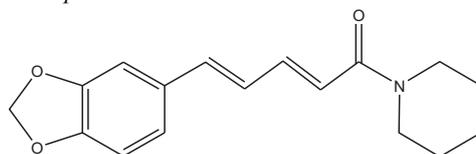


Fig. (4). Structure of Piperine.

5. ANALYTICAL METHODS AND TECHNIQUES FOR DETERMINATION OF PIPERINE

From the commencement of any official pharmaceuticals analytical assay methods were included in compendia monographs with aim to characterize the drug molecule. In recent years, the assay methods in monographs include titrimetry, spectrometry, chromatography, electrophoresis and other analytical methods can be seen in literature. An analytical method plays an important role from the stage of drug development to marketing. Thus, in the field of pharmaceutical research, the analytical investigation of any active constituent, intermediates, drug products, drug formulations, degradation product and biological samples is very important. Considering these analytical principles, chemical degradation, transformation, analyses by spectroscopic methods have been extensively useful in the characterization of piperine analogues. Thus, in case of amides which possess full unsaturation in their hydrocarbon chain or partly saturated hydrocarbon chain which possess an α, β -unsaturated amide carbonyl chromophore. It was observed that the IR spectrum displays absorption bands at 1650 (α, β -unsaturated amide carbonyl), 1605 (conjugated trans CH=CH), 1000 (styryl bond) and 925 (methylenedioxy group), while the perhydro- and the $\Delta \beta, \gamma$ -dihydropiperine and related amides lack the band at about 1605 [38]. The typical ^1H spectroscopic analysis of piperine analogs by NMR, UV, MS fragmentation had been extensively reported and discussed by a number of workers in the past few decades. The ^1H NMR signals are reported in low and as well as in high field region. Both the regions shows significant peaks at chemical shift value of 6.25, 6.65-7.65 for ethylenic and aromatic protons and at chemical shift value at 5.96 for methylenedioxy protons, as recorded for piperlonguminine, piperine, wisanine, trichostachine and sylvatine [37, 39, 40]. The UV absorption peaks for piperine type chromophore is at 250, 304, 378 nm irrespective of the aliphatic amino moiety such as piperine and piperlonguminine which display identical UV characteristics. However, tetrahydropiperine and its analogues have absorption peak at 232 and 285 nm which are very close to 3, 4-methylenedioxybenzenes [38, 40].

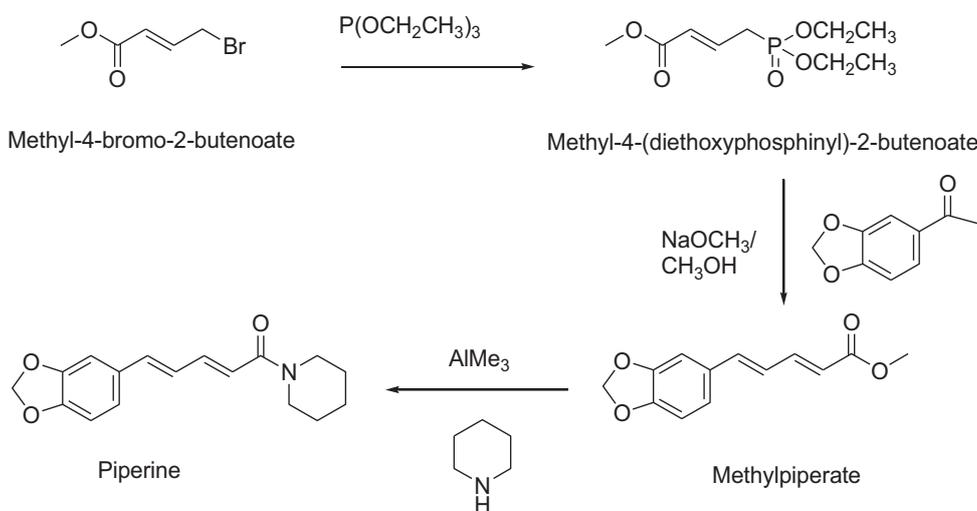


Fig. (5). Synthesis of Piperine from Methyl-4-bromo-2-butenate.

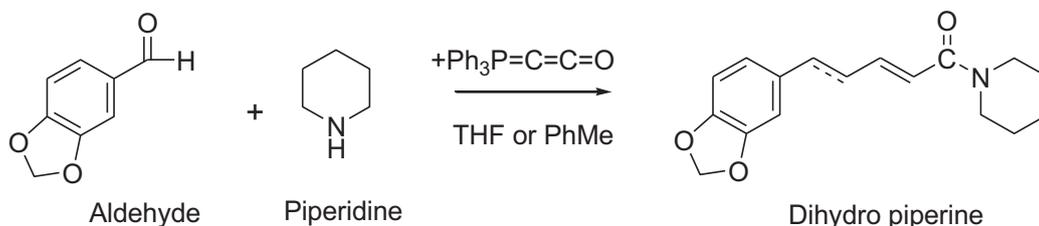


Fig. (6). Three-component reaction between aldehydes, amines and ketylenetriphenylphosphorane.

The mass spectra of piperine analogs, including piperine, sylvatine, trichostachine, piperlonguminine were shows M^+ at 201 (C-N bond), 135 (formation of methylene dioxy tropylium ion) and the base peak at 173 and 172 representing loss of -CO (28) from m/e 201 which is followed by the loss of a hydrogen atom, respectively (Fig. 7) [36, 41]. Thus, to differentiate the conjugation and non-conjugation of the aromatic ring with the amide carbonyl function present in piperine and related amides is characterized by IR and UV absorptions and in the MS fragmentation patterns (Table 1). This is exemplified by the reported spectral data for guineensine and sylvatine that the peak at m/e 161 is for guineensine and related Piper amides, but does not for sylvatine and piperine (Table 1), (Fig. 7) [40, 42].

Table 1. UV, IR, MS spectral data for guineensine and sylvatine.

Compounds	UV spectral data							
	Guineensine	$\lambda_{\text{max}}(\text{Ethanol})$	214	261	302			
	Log C	4.15	4.92	3.81				
Sylvatine	$\lambda_{\text{max}}(\text{Ethanol})$	-	259	304				
	Log C	-	4.69	3.97				
IR spectral data (cm^{-1})								
Guineensine		3300	1655	1630	1605	1545	1000	965 925
Sylvatine		3279	-	-	1605	-	1000	- 922
MS fragment mass ions (m/e)								
Guineensine	$383(M^+)$	248	161	135	131	103		
Sylvatine	$383(M^+)$	201	173	172	171			

scalding heat as well as pain. This study also concludes that the length of carbon chain in piperine amides effects the agonistic potential of the same where as structure changes in double bond and in stereochemistry of aliphatic chain of the prepared amides didn't effect or change the potency or efficacy which indicates the presence of high level of rigidity or planarity in the piperine molecule. It was also observed that the opening of methylenedioxy ring opening or change in the heterocyclic nucleus of the parent molecule, piperine reduces or abolishes the biological response. Furthermore, piperine amides which are inactive or doesn't possess any agonistic potential, which were further investigated for antagonist activity; did not display any activity [44].

Quantitative structure activity relationship (QSAR) analysis of new chemical entities obtained from natural and synthetic one has been performed in order to generate highly accurate model as inhibitors of effluxpump NorA for *Staphylococcus aureus*. To generate the model variables are selected by genetic function approximation method in Cerius 2.

Among them, various types of descriptors were considered; out of which partial negative surface area of the compounds, area of the molecular shadow in the XZ plane and heat of formation are important descriptors responsible for describing the activity of *S. aureus* NorA efflux pump inhibitors.

This theoretical approach indicates that on increasing the exposed partial negative surface area, the inhibitory activity of the compound also increases against NorA whereas on increasing the area of the molecular shadow in the XZ plane decreases the inhibitory activity. However, the model relates and explains the relationship between heat of formation and inhibitory potential but the generated model doesn't able to predict the activity of new compounds it only explains the important regions of the molecules quantitatively [45].

7. BIOLOGICAL ACTIVITIES

Piperine has a broad spectrum of biological properties, many of them have been confirmed by *in vivo* and *in vitro* studies. Piperine contains three major moieties or sites in their structure which are found to be responsible for various bioactivities. Thus, a brief description of some pharmacological activities is provided as best.

7.1. Effects on CNS and Nerve Conductivity

Earlier reports showed that both Pepper (Black and Long) have been used as nervine stimulants. Previous studies have shown that pepper can stimulate CNS activity in various experimental animals [46 - 48]. The research concludes that piperine is responsible for the analeptic activity which may expressed through due to its effect on nerve impulse transmission in the brain stem. Recently, pharmacological action of piperine and capsaicin has been proved to be shown due to its interaction with various transmitters, *i.e.*, neuropeptides: substance P, neurokinins and calcitonin gene related peptide. These neurotransmitters are the agents of nerve transmission or communication present in various parts of the body [49 - 55].

Interaction of piperine and capsaicin with nerve transmissions comes into existence due to various studies carried on recently discovered Vanilloid receptors [56]. Vanilloid receptors are generally known as the group of the receptors which are located in both central and peripheral nervous systems and can accept or bind them with naturally occurring compounds having the chemical structure similar to vanillin *e.g.* piperine, capsaicin and gingerols.

Vanilloid compounds like piperine bind to specific receptor sites which results in a decreasing the levels of transmitters of pain sensation such as substance P, and certain amino acids like glutamate and aspartate [56]. Kawada *et al.* in another study concludes that Piperine may also be involved in neuroregulation process by stimulating the secretion of catecholamine neurohormones, especially epinephrine [57]. It may also affect both CNS and peripheral nervous system function by altering or modifying the blood levels of some neurotropic and muscle relaxing compounds [58, 59]. Piperine also potentiates barbiturate (hexobarbital) –induced sleeping time in various experimental animals [58, 59].

It was equally effective in counter acting respiratory depressions induced by barbiturates in mongrel dogs [60] when compared with known analeptic drugs such as metrazol and nikethamide. It was also observed that piperine had more prolonged action of reversing the respiratory depression induced either by morphine or by barbiturates. Another study shows that piperine possesses promising CNS action when it fed to rats decreases the pain perception relieving β -endorphins in brain [61]. Recently, an interesting study shows that piperine was also effective in mood and cognitive disorder [62]. Piperine and their derivatives showed anticonvulsant action which had been demonstrated in mice and rats [63, 64].

7.2. Antioxidant Property

Piperine, naturally occurring spice component have good potential as antioxidant and hence utilized in nutritional and therapeutical preparations [65, 66]. Piperine is used as co-adjutant for both treating as well as preventing the aging process and its related conditions like atherosclerosis, hypertension, diabetes, tumors, obesity, and overweight, hypertriglyceridemia, hypercholesteromia, skin aging, alopecia, panniculopathia (cellulite), osteroporosis, cerebral aging (Alzheimer, Parkinson, senile dementia *etc.*) and loss of memory, stress, depression, menopausal syndromes and benign prostate hypertrophy [67]. Another study concludes that against diabetes induced oxidative stress can be protected with piperine treatment for 14 days using diabetes mellitus as a model of oxidative damage [68].

7.3. Effect of Piperine on the GIT and Broncho-Pulmonary System

Piperine promptly affects the nutrient absorption as well as the absorption of gastrointestinal xenobiotics by exerting the effect on intestinal, liver and tissue metabolism. It was, however, proven that piperine form polar complexes with xenobiotics and nutrients, thus act as a polar molecule. Hence the compounds have proper partitioning due to this they are able to cross the membrane barriers [69, 70]. The studies also reports neuroregulation of the entire GI tract [71 - 73] was affected by piperine as it interacts directly with the intestinal epithelial layer which further affects the absorption of food, nutrients and drugs [74, 75]. Piperine also inhibits the gastric emptying and GIT in rats and mice [76, 77].

7.4. Piperine and its role in the Metabolism of Xenobiotics in the Liver

Bioenhancers are drug facilitators which itself don't show any drug activity, but when given in combination it enhances the activity of drug molecules which includes: a) increasing the bioavailability of the drug molecule across the membrane. b) Potentiating the drug molecule by conformational interaction. c) Act as a receptor for drug molecule. d) By making target cells more receptive to drugs.

Literature concludes that piperine was used as effective bioavailability enhancer, inhibits the human P-glycoprotein and CYP3A4 a class of enzyme belonging to cytochrome P450 family [78] and enable the particular molecule to remain in biological system for much longer period. In various experimental studies, it has been shown that piperine when compounded with different molecules (drugs) enhances the bioavalibility of β - lactumantibiotics [79, 80], amoxicillin trihydrate and cefotaxime sodium [81], paeoniflorin [82], rifampicin [83, 84], phenytoin [85], oxyphenolbutazone [86], nimesulide [87] and NSAIDS [88] or derivatives significantly. Co-administration of piperine reduces nephrotoxicity [89] and the availability of a catalytic iron source in glomeruli for treating glomerular disorders [89], inhibits prostate specific antigen production [90], in a breast cancer cell lines, BT-474 and a prostate cancer cell line, transfected with the human androgen receptor DNA, PC-3 (AR)2.

Piperine, tetrahydropiperine, its analogs and derivatives also act as bioavailability enhancer of various nutrients including vitamins, β -carotene and selenium [78] and pharmaceuticals [91]. Various *in vitro* and *in vivo* studies concludes that the biotransformation of both water soluble and lipid soluble xenobiotics catalysed by pulmonary cytochrome P450 was likely to be affected or inhibited by presence of piperine [92]. Table 2 shows example of various drugs which on combination with piperine act as bioenhancer. Recently the number of scientific groups reports that Bioperine (98% pure piperine), standard extract of black pepper increases the gastrointestinal absorption of β -carotenes in humans [93] and thus proves clinically bioperine acts as an excellent nutrient bioavailability enhancer of curcumin and beta carotene [93, 94]. Piperine supplemented orally when evaluated in rats causes the inhibition of hepatic mixed function oxidase enzyme, hepatic aryl hydrocarbon hydroxylase (AAH) [95, 96]. Inhibition of these enzymes results in increasing the availability of numerous compounds absorbed in GI tract [92, 96 - 98]. Piperine from Black pepper also increases the plasma levels of co-enzymes Q10 [99] and serum response of beta carotenes followed by oral supplementation [100] and thus proves to be thermogenic by nature.

Table 2. Bioenhancer effect of piperine with some medicines.

Drug	Class	References
Rifampicin	Bactericidal antibiotic	[84]
Isoniazid	Antibacterial agent	[143]
Pefloxacin	Antibacterial	[144]
Tetracyclines	Broad-spectrum antibiotic	[145]
Sulfadiazine	Sulphonamide	[145]
Oxytetracyclines	Broad-spectrum antibiotic	[146]

(Table 2) contd....

Drug	Class	References
Ampicillin	β -lactam antibiotic	[147]
Norfloxacin	Antibacterial agent	[147]
Nevirapine	NNRTI	[148]
Metronidazole	Nitroimidazole antibiotic	[149]
Diclofenac Sodium	NSAID's	[150]
Pentazocine	Opioid analgesic	[150]
Nimesulide	NSAID's	[151]
Phenytoin	Antiepileptic	[152]
Pentobarbitone	Short-acting barbiturate	[97]
Propranolol	β -adrenoceptor blocker	[153]
Theophylline	Bronchodilators	[153]
Carbamazepine	Anticonvulsant	[154]

7.5. Analgesic and Anti-inflammatory Activity

Piperine also shows good potential for anti-inflammatory activity in a model with hind paw tissue swelling and arthritis in rats [101]. Moreover, piperine administration reduces the histologic damage and myeloperoxidase activity in the pancreas and ameliorates numerous parameters which include the pancreatic weight to body weight ratio, as well as serum levels of amylase, lipase and trypsin activity. Studies with piperine pretreatment concludes that it reduces the production of tumor necrosis factor (TNF)- α , interleukin (IL) - 1b, and IL-6 during cerulein-induced acute pancreatitis (AP). *In vivo* results also prove that piperine reduces cell death, activity of enzyme amylase and lipase and production of cytokine in isolated cerulein-treated pancreatic acinar cells. In addition, piperine also inhibits the activation of mitogenactivated protein kinases [102].

In another study also proves the anti-inflammatory action of piperine comparable with curcumin derived from *Curcuma longa* [103]. Along with anti-inflammatory activity piperine also shows antiarthritic activity [104]. Piperine was also isolate from the bark of *Careya arborea*, found to possess significant central and peripheral analgesic activity at oral doses of 10, 20 and 30 mg/kg body weight against acetic acid induced writhing in mice. However, piperine shows prolongation of tail flicking time at doses of 20 and 30mg/Kg body weight by radiant heat method in mice [105]. Tasleem *et al.* evaluate and compare the analgesic and anti-inflammatory activity of pure compound, piperine along with hexane and ethanol extracts of *Piper nigrum* L. fruit in mice and rats and concludes that it possess potent analgesic and anti-inflammatory activity at different doses by different methods [106]. Piperine intraperitoneally shows at 20 and 30 mg/kg by hot plate reaction test and acetic acid test in mice using indomethacin as a standard drug for reference [107].

7.6. Antidepressant Potential

Piperine and its derivative, antiepilepsirine possesses antidepressant activity which was investigated in the depressive models like forced swimming test and tail suspension test. During this study determination of brain monoamine levels and the activities of monoamine oxidase A and B were carried out. The results show that in an assay of monoamines, chronic antiepilepsirine administration significantly elevates the dopamine level in striatum, hypothalamus and hippocampus, and also increases the serotonin level in the hypothalamus and hippocampus. In contrast, chronic treatment only with piperine enhances the level of serotonin in the hypothalamus and hippocampus but didn't show any significant influence on the dopamine level. Moreover, both antiepilepsirine and piperine didn't show any effect in the nonadrenaline level particularly in brain areas. The MAO activity assay also indicates that piperine and antiepilepsirine shows a minor MAO inhibitory activity. Liet in his study says that antidepressant potential of piperine was to be mediated *via* the regulation of serotonergic system, whereas antiepilepsirine antidepressant action might be mediated *via* dual regulation of both serotonergic and dopaminergic systems [108]. In another study, piperine shows antidepressant like activity and cognitive effect during entire duration of treatment in Wister male rats at various doses ranging from 5, 10 and 20 mg/kg/day [62].

7.7. Piperine as Efflux Pump Inhibitor

In 2006, Inshad Ali Khan reported that piperine (a trans trans isomer of 1- piperoyl-piperidine), a major constituent of *Piper nigrum*, when administered in combination with ciprofloxacin markedly reduces the MICs and also prevents the mutation concentration of ciprofloxacin for *Staphylococcus aureus*, including methicillin-resistant *S. aureus*. The

enhanced accumulation of ethidium bromide and thus decreased efflux of same in the wild-type and mutant (CIPr-1) strains was observed in the presence of piperine which suggest its involvement in bacterial efflux pumps inhibition and thus prove its role as an Efflux Pump Inhibitor [109].

7.8. Renal and Hepatic Effect of Piperine

Presently a study by Begum *et al.* 2015 investigates the effect of Piperine and Metformin alone and in combination in gentamicin induced renal and hepatotoxicity [110] and the results suggest that the Piperine (50mg/kg and 100mg/kg), Metformin (100mg/kg) and a combination of Piperine (50mg/kg) and Metformin (50mg/kg) proves to be beneficial in treating Gentamicin induced renal and hepatotoxicity.

7.9. Antiplatelet Effect of Piperine

Fruits of the *Piper longum* contain piperine, piperonaline, piperoctadecalidine, piperlongumine which shows inhibitory potential on washed rabbit platelet aggregation [111]. All these acid amides shows dose-dependent inhibitory activity on washed rabbit platelet aggregation and the acid amide Piperlongumine shows stronger inhibitory effect than other acid amides to rabbit platelet aggregation induced by collagen, AA and PAF.

7.10. Effect on the Lipid Peroxidation

Study carried out by Dhuley in 1993 concludes that the pretreatment with piperine reduces the liver lipid peroxidation, acid phosphatase and oedema induced by carrageenin in rats. Thus the study suggests that the liver enzymes are inhibited but they are non specific in nature [112]. Lipid peroxidation content, measured as thiobarbituric reactive substances (TBARS), was increased with piperine treatment although conjugate diene levels were not altered in a study carried out to determine the toxicity of piperine *via* free-radical generation by determining the degree of lipid peroxidation and cellular thiol status in the rat intestine. The study suggests that increased TBARS levels may not be a relevant index of cytotoxicity, since thiol redox was not altered, but increased synthesis transport of intracellular GSH pool may play an important role in cell hemostasis [113]. Oxidative stress occurs in association with painful exacerbations of chronic pancreatitis and antioxidant supplementation appears to benefit this condition. Thus in another study, oral therapy of curcumin with piperine reverses the lipid peroxidation in patients with tropical pancreatitis. It was also observed that there was a significant reduction in the erythrocyte MDA levels and significant increase in GSH levels. There was no corresponding improvement in pain [114].

7.11. Effect of Piperine on Lipid Profile

A study carried out by Peela focuses on the individual effect on biochemical parameters like blood sugar and lipid profile before and after the administration of piperine and concludes that it beneficially effects of piperine in lowering the level of triglycerides but increasing the HDL cholesterol. This study has shown it does not have any role in reducing blood sugar and total cholesterol [115]. Piperine also prevents the accumulation of plasma lipids and lipoproteins significantly by modulating the enzymes of lipid metabolism [116]. In 2011 a study explores the effect of piperine in obesity-induced dyslipidemia. It concludes that the supplementation of piperine with high fat diet significantly reduces not only body weight, triglycerides level, total cholesterol, LDL, VLDL, and fat mass at a small doses of 40 mg/kg but also increases the HDL levels without causing prominent change in food intake. This action may be guessed to be involvement of MC- 4 receptors [117]. Piperine effects the lipid composition and some lipogenic enzymes in the rat testis. An oral dose of 5 and 10 mg/kg body weight depletes the total lipid content which was mainly due to the diminution of the phospholipid concentration and free cholesterol level where as there was marked increase in total cholesterol and cholesterol ester. Similarly total glyceride level and triacyl glycerol level shows a significant increase at an expense of diacyl glycerol in rats treated with the high dose of piperine. In contrast, Lipogenic enzymes, malate dehydrogenase (MDH), malic enzyme (ME) and isocitrate dehydrogenase (ICDH) were inhibited by the high dose and only MDH and ME activities were inhibited by the low dose treatment of piperine [118]. The various other properties possessed by piperine has been mentioned in Table 3.

8. EVIDENCE TO PROVE PIPERINE AS A BIOENHANCER

Recently the piperine action as bioenhancer has been found by Indian Institute of Science, Bangalore using *Mycobacterium smegmatis* as the test organism [73]. The study provides an interesting observation that piper alone even at high concentrations does not inhibit the growth of mycobacteria but it shows a remarkable growth reduction /inhibition on the microorganism and this inhibition is higher than that of rifampicin alone. As rifampicin acts on RNA

polymerase where as piperine abrogates the non specific transcription which is catalysed by *M. smegmatis* RNA polymerase. When RNA polymerase was purified from a rifampicin resistant strain of *M. smegmatis*, the enzymatic activity, otherwise resistant to rifampicin, found 12 to be significantly decreased in presence of piperine along with Rifampicin.

Table 3. Some important role of piperine.

Different effect of Piperine	References
Piperine inhibit pulmonary cytochrome P450 activities	[92]
Piperine inhibit UDP-glucose dehydrogenase and UDP- glucuronyl transferase	[98]
Piperine shows antileishmanic activity	[155]
Piperine increases serum response of β -carotene	[100]
Piperine inhibit aflatoxins B1 (AFB ₁)biosynthesis	[156]
Piperine shows antimalarial activity	[157]
Piperine reduced the production of aflatoxins	[158]
Thermogenic action of piperine <i>via</i> adrenal catecholamine secretion	[159]
Piperine inhibit monoamine oxidase	[160]
Piperine inhibit ascorbate-Fe ⁺⁺ -induced lipid peroxidation	[161]
Piperine protected against oxidative stress induced carcinogenesis	[162]
Piperine modulated membrane dynamics and permeation characteristics	[162]
Piperine shows chemopreventive effectin carcinogenesis	[163, 164]
Piperine inhibited mitochondrial oxidative phosphorylation	[165]
Piperine exerted protection against t-butyl hydroperoxide	[166]
Piperine protects cisplatin-induced apoptosis via heme oxygenase-1	[167]
Piperine potentiate hepatotoxicity of carbon tetrachloride in rats	[168]
Inhibition /quenching of super oxides and hydroxyl radicals by piperine	[169]
Piperine reduces high fat diet induced oxidative stress	[170]
Anti-metastatic activity of piperine on lung metastasis	[171]
Piperine inhibits platelet aggregation as a TXA ₂ receptor antagonist	[172]
Piperine decreased mitochondrial lipid peroxidation	[173]
Piperine alleviates hypertension induced by NO synthase inhibition	[174]
Piperine reduced D-galactosamine induced hepatotoxicity	[175]
Piperine inhibited cholesteryl ester (CE) synthesis	[176]
Piperine enhances bioavailability of the tea polyphenol	[177]
Piperine shows anti mutagenic activity	[178, 179]
Piperine shows anti-thyroid activity	[180]
Piperine modulates hormonal and apo lipoprotein profiles	[181]
Blood pressure lowering and effects of piperine	[182]
Piperine shows cytoprotective and immunomodulating properties	[183]
Piperine protects against neurodegeneration and cognitive impairment	[184]
Piperine inhibit mitochondrial dysfunction and cell death in PC ₁₂ cells	[185]
Piperine shows antibacterial and fungicidal activity	[186, 187]
Piperine shows insecticidal activity	[188, 189]
Piperine stimulates melanocyte replication <i>in vitro</i> and useful in treating the depigmenting disease, vitiligo.	[190, 191]
Piperine shows antidiarrhoeal activity	[76, 192]

The study carried out by Reen's observes and concludes that methylenedioxyphenyl ring founds to be responsible in inhibiting the drug metabolizing enzymes [119]. Another study by Atal in 1985 concludes that we can enhance the *in-vivo* drug bioavailability by inhibiting the hepatic and non hepatic drug metabolizing enzymes [59]. The property of enhancing the bioavailability of drugs is partly due to the increased blood supply to the intrinsic vessels as a result of local vasodilation. In case of enzymatic activity, Glucoronyl transferase inhibits the endogenous UDP glucuronic acid content and by decreasing transferase activity [119]. One more mechanism of action of piperine was also explains by IJMM, Jammu, which states that Piperine act as a cell membrane modulator and thus helps in transportation of the drugs molecules across the barriers. It was speculated that piperine may also called as thermotonic as it increases the GIT absorption of certain nutritional substances and thus helpful in production of local thermogenic action. To enhance the mechanism for drug bioavailability, following possible explanations' are:

- a. Increased blood supply to GIT,
- b) Increased enzymatic activities like gamma-glutamyl transpeptidase
- c) Non-specific mechanisms inhibiting enzymes involving in biotransformation of drugs, preventing their inactivation and elimination [70, 120].

9. METABOLIC IMPLICATIONS OF PIPERINE

A study proves that Piperine interacts and interferes both *in vitro* and *in vivo* with the metabolism and degradation related enzymes and thus act as a nonspecific inhibitor of drug metabolism. Piperine inhibits a series of enzymes mainly related to P-gp and cytochrome P 450 family other enzymes are: Aryl hydrocarbon hydroxylase (Microsomal enzyme system), Ethyl morphine-N demethylase, 7-Ethoxycoumarin-O-de-ethylase, 3-Hydroxy-benzo(a)pyrene glucuronidase, Uridine di phosphate glucose dehydrogenase (UDP-GDH), Uridine di phosphate glucuronyl transferase (UDP-GT), 5-Lipoxygenase (5-LOX) and Cyclo-oxygenase-I (COX-I) [121].

10. METABOLIC CHANGES AFTER ADMINISTRATION WITH PIPERINE

The study concludes that a supplementation of piperine to fat, carbohydrate, fructose and cornstarch fed rats normalizes the blood pressure, improve glucose tolerance and reduce plasma parameters of oxidative stress and inflammation. In addition to this, it also improves the liver function [122].

11. PHARMACOKINETICS

To study the pharmacokinetic parameters and tissue distribution of piperine, lipid nanospheres of piperine (LN-P), pegylated lipid nanospheres LN-P-PEG and positively charged stearylamine LN-P-SA were prepared by process of homogenization which was further followed by ultrasonication and evaluated on male albino mice. The pharmacokinetic parameters of LN-P-PEG and LN-P-SA were: AUC(0-24): 372.1 +/- 71.6 and 162.2 +/- 36.4 microgram/hour/ml, clearance 13 +/- 2.5 and 32 +/- 7.5 ml/hour, Cmax: 24.7 +/- 1.5 and 22.3 +/- 1.0 microgram/ml, Vd: 0.45 +/- 0.02 and 0.66 +/- 0.06 liter/Kg. Pharmacokinetics of lipid nanospheres of piperine shows a biexponential decline with significantly high AUC, lower rate of clearance with a smaller volume of distribution than piperine [123].

10. MARKETED PREPARATIONS OF PIPERINE

Ayurvedic formulation: ChitrakadiVati [124], Trikatu Churna [125, 126], Pippli Churna [127], Sitopaladichurna (STPLC) [128], Ajmodadichurna (AJC) [129, 130], Triphalaguggulu [131], Eladi Gutika [132], LasunadiVati, Marichyadivati and Kaphaketu rasa [133]. Unani formulation: Hab-e-Azarakhi [134], Jawarish-e-Bisbasa [135], Habb-e-Khardel [136]. Dosage forms 1) Vista Nutrition Curcumin with Piperine (Capsule) Description: Vista Nutrition Curcumin with Piperine capsules has anti-oxidant, anti-inflammatory effects. It contains curcumin and piperine that restrains the enzyme called CYP3A4 to increase the oral bioavailability of compounds. Vista Nutrition Curcumin with Piperine helps in maintaining the healthy liver and protecting the brain cells. 2) Zenith Nutrition Curcumin with Piperine (Capsules) Description: Zenith Nutrition Curcumin with Piperine contains curcumin and piperine. The active component of turmeric (curcumin) is responsible for its rich color and potential health benefits. The powerful antioxidant helps in protection of cells from free radical damage, in maintaining a healthy inflammatory response, protection of brain cells, in maintaining a healthy liver even under challenging circumstances. Standardization of preparation also ensures the consistent levels of active ingredients in every dose.

12. CLINICAL STUDIES

The clinical studies of piperine shows that it may enhance the bioavailability of resveratrol a substance commonly found in red grapes, peanuts and chocolate which help in translating the potential benefit of the same to humans. Resveratrol (3, 5, 4'-trihydroxystilbene) is chemically a phytoalexin possess numerous health-promoting properties in pre-clinical studies. On comparing the resveratrol alone, combination with piperine increases the degree of exposure of resveratrol to 229%, while exposure to the compound principal metabolite decreased by about 80%. Piperine enhances the resveratrol pharmacokinetic parameters *via* inhibiting its glucuronidation, and hence thereby slows the process of elimination [137]. Recent studies, in collaboration with Oregon Health and Science University (OHSU) dermatologists, the combination piperine with narrow band ultra violet B (NBUVB) was applied to National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS) to fund a Phase I clinical trial for vitiligo disease. Moreover, the reviewers expressed enthusiasm for piperine as a novel treatment for vitiligo, and for the design of the clinical trial, a major concern was piperine unknown effect on melanoma development, particularly if used

in conjunction with UVB. This concern is a major hurdle to the future clinical investigation of piperine in vitiligo, and clearly must be addressed. Therefore the effect of piperine, alone or with UV radiation, on melanoma development using the HGF-BL6 mouse model of melanoma was investigated. However, the result shows, despite its stimulatory effects on normal melanocyte proliferation, PIP will not promote, and may even reduce, melanoma formation in a murine model of UV-induced melanoma [138, 139].

13. TOXICITY

Piperine is used as spice and nutrient enhancer. The study conclude that, consecutive administration of piperine (2.25 and 4.5 mg/kg, p.o.) for five days causes a significant reduction in total leukocyte counts, increases the percentage of neutrophils and suppresses the mitogenic response of B-lymphocyte to lipopolysaccharide in swiss male mice. Moreover, the treatment at higher dose results into significant decrease in the weight of spleen, thymus and mesenteric lymph nodes.

However, at lower dose (1.12 mg/kg, p.o.) it may be considered as immunologically safe [140]. The previous research concludes and suggests that piperine should be co-administered with drugs *i.e.* P-gp substrates, particularly for patients whose diet heavily relies on Pepper.

Piperine concentration ranging from 10 to 100 μ M, inhibits P-gp mediated efflux transport of [3H]-digoxin across LMDR1 and Caco-2 cell monolayers. This acute inhibitory effect depends on concentration of piperine with abolishment of [3H]-digoxin polarized transport which was attained at 50 μ M of piperine. In contrast, the prolonged (48 and 72 h) co- incubation of Caco-2 cell monolayers with piperine (50 and 100 μ M), increases P-gp activity through an up-regulation of cellular P-gp protein and MDR1 mRNA levels. The up-regulated protein was functionally active, as it is demonstrated with a higher degree of [3H]-digoxin efflux across the cell monolayers, but the induction was totally readily reversed by the removal of piperine as spice from the culture medium. Oral administration of piperine (112 μ g/kg) for 14 consecutive days increases intestinal P-gp levels in male wistar rats. Thus, it was observed that concomitant reduction in the rodent liver P-gp whereas kidney P-gp level remains unaffected [141].

It was well that Cadmium (Cd) is an industrial and environmental ubiquitous pollutant, and it is toxic to several tissues, most notably hepatic and renal acute administration results its chronic exposure thus, a study by Khandelwal evidences that piperine at 2.5 mg/kg/day significantly decreases the hepatic and renal Cadmium levels in mice [142].

14. CONCLUSION AND FUTURE ASPECTS OF PIPERINE

In the present review, an attempt has been made to congregate the erudition of versatile molecule, PIPERINE. Although it have medicinal applications from time immemorial, but today's need is to develop modern drugs with effective extensive investigation for its bioactivity, mechanism of action, pharmacotherapeutics, and toxicity and after proper standardization and clinical trials. Reviewed interest among the researchers all around the world in the structural modification and synthesis of novel analogues of the privileged molecule piperine is attributed to the wide array of biological activities it possesses. It appears to top in the list of bioenhancers as it has been used as bioenhancer for Allopathic, Ayurvedic and Unani drugs. Several therapeutically as well as industrially useful preparations have been marketed which generates encouragement among the scientists in exploring this medicinal important moiety. As it is very well evident from the literature that piperine has got tremendous potential, thus the appropriate modification in the molecule and synthesis of its analogues to attenuate the toxicity with better economic investment and with good therapeutic utilization presents greater benefit particularly in various treatments and therapies.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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