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An Overview of Bioactive Alkaloid, Semi-Synthetic Analogs, Mechanism of Action and Structure-Activity Relationship of Piperine as Antioxidant

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Piperine, a natural alkaloid obtained from black pepper exhibit a variety of pharmacological activities like antioxidant activity and in this article, the mechanism of the antioxidant, structure-activity relationship of piperine as an antioxidant and various schemes of derivatives of piperine as antioxidants were discussed.

Keywords: Piperine, Piperic acid, Antioxidant, Pharmacological, Piperine, Free radicals.

INTRODUCTION

In recent decades, oxidation processes and the importance of free radicals in biological systems have received wider attention. The chemical process of oxidation is the transfer of electrons from a substance to an oxidizer [1]. Antioxidants halt chain reactions by removing free radical intermediates and stopping new oxidation processes by becoming oxidized themselves [2,3]. Antioxidants have been defined in biological systems as any molecule that significantly slows or stops the oxidation of an oxidizable substrate when present at low concentrations compared to those of the oxidizable substrate [4]. There is a rising interest in antioxidative chemicals because they have the potential to quench free radicals and so protect cells and tissues from oxidative damage [5]. Based on the source of antioxidants they are basically of two types natural and synthetic [6]. Natural antioxidants are primarily phenolic which can break the cycle of radicals and convert them into more stable molecules [7].

Nature belongs to plants and plants have secondary metabolites which are plentiful source of bioactive chemicals and scientific community has worked together to encourage the development of new plant based medicines [8]. The medical uses of plants are one of the most effective criteria used by the pharmaceutical industry in discovering innovative therapeutic molecules for various fields of biomedicine, piperine is obtained from black pepper is one of them and consist of various pharmacological activities [9]. Scientists have been working for many years in their research work to know the antioxidant activity of piperine and its derivatives and still research experiments with synthetic route is going on to find its strongest antioxidant activity [10,11]. Piperine, *Piper nigrum* L., a member of the Piperaceae family, is one of the most commonly used spices. Piperine is the amide of 5-(2, 4-dioxymethylene-phenyl)hexa-2,4-dienoic acid with piperidine, gives black pepper as its strong characteristic fragrance [12]. Two piperine equivalents derived from *Piper nigrum* are piperanine and piperettine [13]. In diet, black pepper is a promising source of natural antioxidants [14] and its constitutents make it an excellent choice for decreasing oxidative stress [15]. Piperine's geographical range includes the Indo-Malayan region, which is home to the *Piper nigrum*. It may be found growing wild in India's tropical rain forests [16].

Extraction: Black and white peppers have two primary components *viz*. volatile (essential) oil and pungent chemicals, which are responsible for the scent and pungency of the peppers, respectively [17]. Pepper oil is obtained by steam distillation of dried peppercorns and devoid of pungent chemicals and consists solely of aromatic and odorous components [18]. Pepper oil is highly regarded in the fragrance business and utilized in high-end hygiene goods, as well as the perfume and taste industries due to its scent. Pepper, on the other hand, is prized as a

condiment all around the world for the pungent and non-volatile chemicals present in the oleoresin, which is a solvent extractable component of black pepper contains specific odour, taste, and pungency. It makes up around 6% to 13% of black pepper [19]. It is generally acquired by extracting powdered pepper repeatedly with volatile organic solvents such as acetone, ether, ethanol, dichloroethane or ethyl acetate, then remove the solvent under decreased pressure to trace amounts [20]. The volatile oils and piperine content of the so-called oleoresin define its organoleptic characteristics and their abundance is dependent on the pepper type and maturation stage, extraction solvent and the extraction conditions [21]. The oleoresin supplied for sale by large manufacturers is said to have 15-20% volatile oil and 35-55% piperine on average [22]. The cost of extraction and purification stages might be as high as 50% to 90% of the final product cost in some situations.

In general, a good extraction technique should be thorough, quick, easy and inexpensive [23]. As a result, the choice of an appropriate extraction technique and extraction solvent has a significant impact on the economic processes. The extraction of piperine using aliphatic and chlorinated hydrocarbons is one of the most used techniques [24]. However, some of the specified solvents aren't selective for piperine, the extract obtained in this manner always contains some significant components like resins and gums. Piperine purity should be 95-98% for medicinal uses [25], as a result, oleoresin extract with a purity of 40-50% has to be purified further. Piperine is purified most often *via* crystallization from aqueous-alcoholic solutions and treatment with aqueous alkali solutions, both of which reduce the piperine output. Dichloromethane, petroleum ether, diethyl ether, alcoholic solvents like ethanol, hydrotrope solutions and ionic liquids are some of the solvents utilized for the piperine extraction. Soaking, maceration and Soxhlet extraction are all traditional solvent extraction techniques [26]. These techniques generally need a long extraction time and/or a high temperature, putting thermosensitive bioactive chemicals at danger of heat destruction. Furthermore, the drawbacks of traditional extraction procedures might be exacerbated by the use of a high volume of solvent and poor extraction selectivity [27].

Researchers have been looking for better extraction procedures to reduce product loss and create bioactive molecules with particular quality features as a result of these disadvantages. Supercritical carbon dioxide (CO_2) extraction, ultrasound assisted extraction (UAE) and microwave-assisted extraction (MAE) are three contemporary piperine extraction methods [28].

Mechanism: Antioxidants react with free radicals in a variety of ways, including hydrogen atom transfer (HAT), single electron transfer (SET) or a combination of both HAT and SET [29]. The HAT reaction is a coordinated movement of a proton and an electron in a single kinetic step [30]. The free radicals take one hydrogen atom from the antioxidant in the HAT processes and the antioxidant becomes a radical [31]. The bond dissociation enthalpy (BDE) is an essential metric in assessing the antioxidant activity in this mechanism. Lower the BDE of the H-donating group in a possible antioxidant, the easier the free radical inactivation process will be (Fig. 1). Single-electron transfer from the nucleophile to the substrate is used to mimic the SET reaction, resulting in a radical intermediate whose destiny may be influenced by a variety of factors [32]. In SET processes, the antioxidant donates an electron to the free radical, becoming a radical cation in the process. In this process, antioxidant's ionization potential is the most significant energetic component in determining the antioxidant's effectiveness [33]. The easier it is to extract electrons when the ionization potential is low [34]. It is difficult to distinguish the difference between HAT and SET reactions. In most cases, these two reactions occur concurrently and the mechanism of the reaction is dictated by the structure, solubility of the antioxidant, partition coefficient and polarity of the solvent [35].

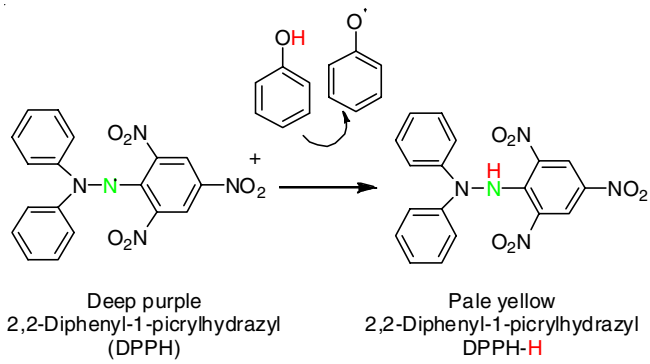
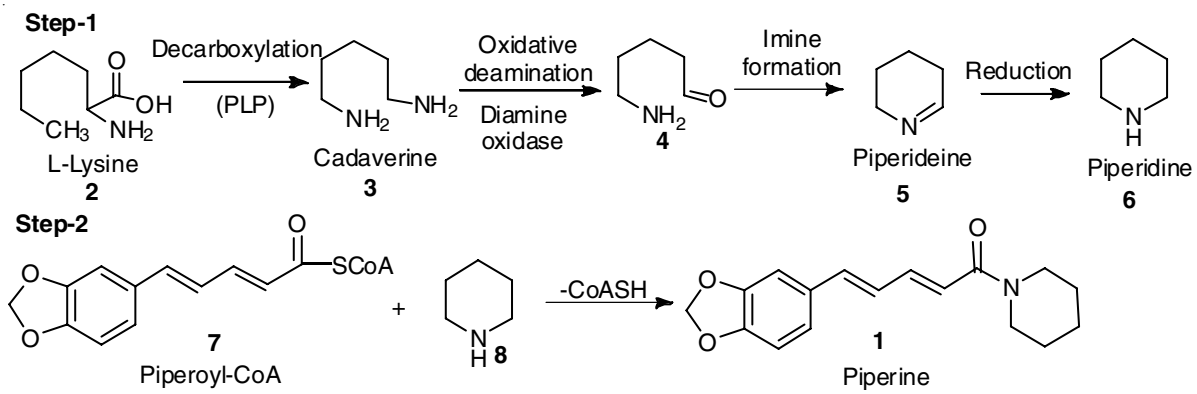


Fig. 1. Antioxidants mechanism by hydrogen atom transfer (HAT)

The indirect antioxidant mechanisms of natural antioxidants, particularly hormesis, are a mechanism that causes the activation of enzymes involved in the innate detoxification pathways and/or the control of vitamin expression [36]. Furthermore, they speculated that natural antioxidants found in plant chloroplasts and mitochondria may make their way into human mitochondria, improving electron transport and oxidative phosphoryl [37].

Biosynthesis of piperine: Piperine belongs to the alkaloid family of auxiliary metabolites, whose production is likely to be triggered by a series of reactions such as decarboxylation, accumulation, cyclization and oxidative deamination [38]. The amino acid precursor L-lysine 2 will be dynamic in the biosynthetic cycle on route to piperine and the entire biosynthetic process is divided into two stages [39,40]. The first phase occurs mostly with the buildup reaction, which includes *N*-heterocycle piperidine and thioester piperoyl-CoA, and provides an opportunity for bunch movement, which is critical for the response [41]. *N*-heterocycle piperidine initiates decarboxylation of the amino acid L-lysine in the presence of pyridoxal phosphate (PLP) to cadaverine, which then proceeds to oxidative deamination by the chemical diamine oxidase to produce the amino aldehyde [42]. This amino aldehyde then set up additional cyclization to produce imine 1-piperidine, which then decreases to piperidine and the subsequent advance, then piperidine then interacts with piperoyl-CoA 7 to provide piperine to the given piperidine [43] (**Scheme-I**).

Chemical synthesis of piperine: For the synthesis of piperine, various synthetic methods have been described, and only few of them will be discussed in this section. In 1995,



Scheme-I: Biosynthetic route of piperine

Sloop [44] described a microscale synthesis of piperine that used allylic bromination of methyl 2-butenoate followed by aldol-like condensation to produce ester, which was saponified to piperic acid. Aminolysis with piperidine was used to synthesize piperine from piperic acid (Fig. 2A). Piperine was synthesized in a very stereoselective manner *via* a two-fold elimination process of β-acetoxy sulphone. The process included combining piperonal-derived sulphone with an aldehyde to produce acetate. This acetate is then subjected to a two-fold elimination process, (Fig. 2B) [45]. Tsuboi & Takeda [46] reported the piperine synthesis in three stages from piperonal (Fig. 2C). Olsen & Spessard [47] described a two-step stereoselective piperine synthesis, where piperic acid was synthesized *via* a vinylogous Wadsworth-Horner modified Wittig condensation of piperonal with the anion generated from methyl (*E*)-4-diethylphosphono-2-butenoate, which was then aminolyzed with piperidine using a methoxide catalyst (Fig. 2D). For an effective synthesis of piperine, Chandrasekhar *et al.* [48] utilized nucleophiles (RMgX and RLi) on aldehyde to sylhydrazones of aromatic and heteroaromatic scaffolds (Fig. 2E). Another approach [49] includes a three-component intermolecular reaction involving aldehydes, amines and ketenylidenetriphenylphos-phorane to produce (*E*)-α,β-unsaturated amides (Fig. 2F).

Structure-activity relationship of piperine as an antioxidant: The molecule's structural characteristics, which include an aromatic ring with a methylenedioxy bridge, a conjugated dienone system and a piperidine ring creating an amide bond, have been thought to be crucial for the molecule's ability to display a wide range of bioactivities [50]. Several changes to the following structural components have influenced piperine's biological characteristics, increasing or eliminating its action in some circumstances (Fig. 3) [51,52].

Piperine derivatives having antioxidant activity: The inhibitory action of novel piperine derivative *viz.* α-benzyl (2*E*, 4*E*)-5-(benzo[*d*][1,3]dioxol-5-yl)-2-cyanopenta-2,4-dienoate (Fig. 4a) is found to be specific for MAO-B. After the synthesis of piperic acid, the derivative of piperine was synthe-sized by reacting methoxy benzene with cyanoacetic acid, pyridine and piperidine at 60 ºC for 30 min [53].

The over-expression of MAO is linked to a variety of neurodegenerative diseases. The piperine derivative developed by computational design has some MAO inhibitory characteristics as well as significant antioxidant activity. The most potent inhibitors of MAO-A are (*N*-(naphthalen-1-yl)penta-2,4-dienamide) and (2-methoxy-4-(prop-2-en-1-yl)-phenyl (2*E*,4*E*)-5-(2*H*-1,3-benzodioxol-5-yl)penta-2,4-dienoate) (Fig. 4b) [52].

Piperine derivatives with phenolic hydroxyl groups (Fig. 4c) are efficacious in preventing AAPH-induced erythrocyte lysis and providing protection to oxidative damaged erythrocytes. Piperine derivatives ((2*E*,4*E*)-5-(2*H*-1,3-benzodioxol-5-yl)-*N*-(4-hydroxyphenyl)penta-2,4-dienamide (2E,4E)-5-(2H-1,3-benzodioxol-5-yl)-N-(2-hydroxyphenyl)penta-2,4 dienamide) and 2*E*,4*E*)-5-(2*H*-1,3-benzodioxol-5-yl)-*N*-(3-hydroxyphenyl)penta-2,4-dienamide) are strong antioxidants, which preserve the intracellular glutathione peroxidase (GSH-Px) [54].

Methyl derivative (3*E*,5*E*)-6-(benzo[*d*][1,3]dioxol-5-yl)-hexa-3,5-dien-2-one piperic acid derivative (Fig. 4d) is obtained after reaction of piperic acid with anhydrous methanol in alkaline medium for 6 h resulted in the formation of the yellow colour crystals of piperic acid . This piperic acid derivative shows a potent antioxidant activity [55].

Piperine derivative with R substituent: The anticancer activity of 4-ketobutyl (2*E*,4*E*)-5-(2*H*-1,3-benzodioxol-5-yl)-penta-2,4-dienoate is also studied (Fig. 4e). Through oxidative and the anticancer activities, 4-(4-nitrobenzoate)piperinoate has low toxicity and anti-tumor impact [39]. When compared to *in vitro* enzymatic studies and *in vivo* studies, the antidepressant impact of piperine and antiepilepsirine (*E*)-3-(benzo-[*d*][1,3]dioxol-5-yl)-1-(piperidin-1-yl)prop-2-en-1-one found that both compounds had modest inhibitory action on MAO-A and B [56] (Fig. 4f). The MAO activity of mouse brain homoge-nates was reduced in a dose-dependent manner by guinensine with IC_{50} values of 3.6 and 139.2 μM, respectively. Positive controls of iproniazid and piperine corroborated the inhibitory actions [57].

A new derivative of piperine 5-(1,3-benzoxazole-6-yl)-1-(piperidin-1-yl)pentane-1,4-dione has a capacity to bind to trigger the *in vitro* signaling cascade Keap1-Nrf2-ARE, which prompted to investigate the beneficial effects of the new derivative on ibotenic acid (IBO)-induced neurological disorders. (Fig. 4g). The antioxidant-responsive element (ARE) and nuclear Nrf2 work together to promote the expression of antioxidant genes. More significantly, a rising amount of data shows that Nrf2 is involved in Alzheimer's disease [43].

Another piperine derivative (Fig. 4h) substantially decreased the amounts of proinflammatory mediators [interleukin-1

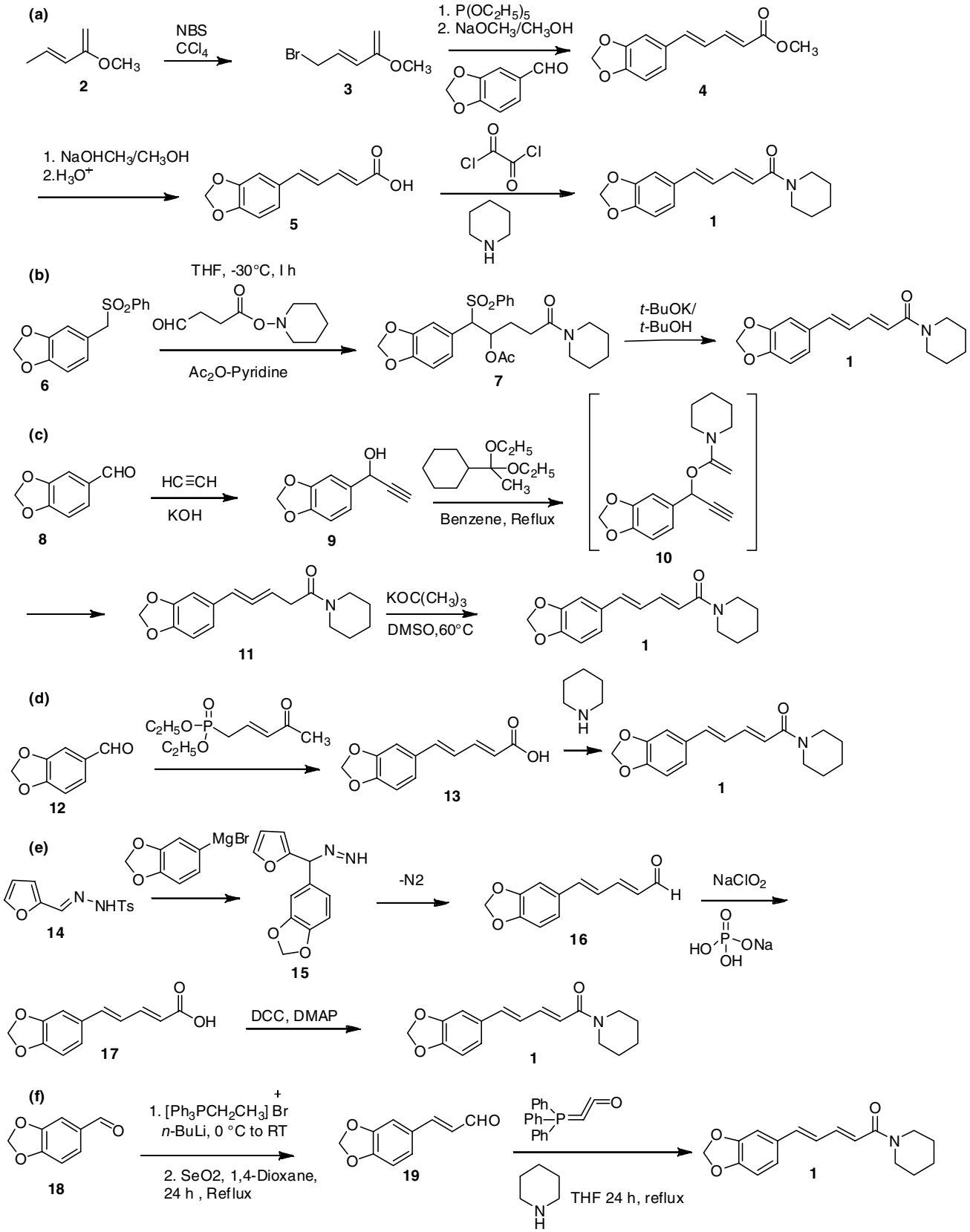


Fig. 2. Various chemical synthetic schemes for the preparation of natural alkaloid piperine (**1**)

(IL-1), tumor necrosis factor (TNF) and prostaglandin-2 (PGE2)] and raised the level of interleukin-10 in all biochemical, inflammatory and parameter tests (IL-10). Piperine's antiarthritis properties were further demonstrated by a reduction in arthritis score and bone histology. The findings stated that piperine's protective impact is mediated by its antioxidant activity, which

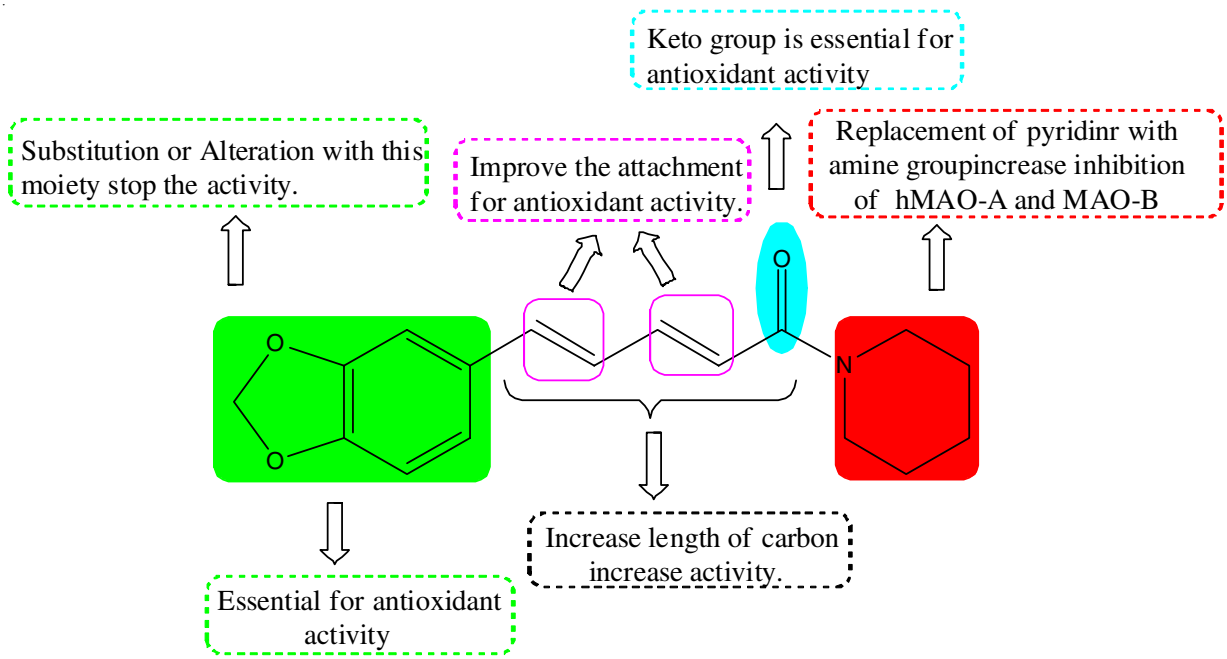


Fig. 3. Structure-activity relationship of piperine and its derivative as an antioxidant

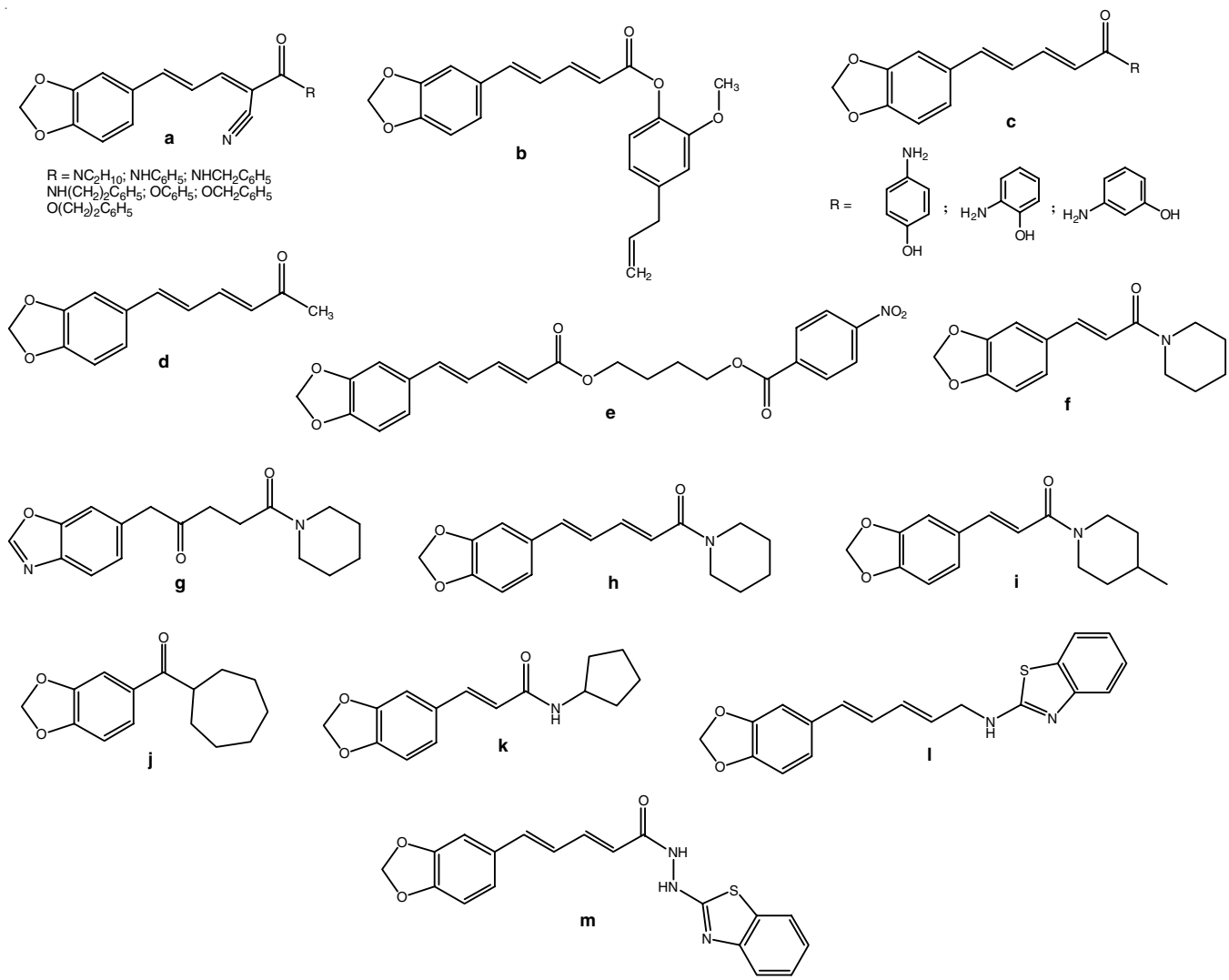


Fig. 4. Structure of various piperine derivatives (a-m)

suppresses lipid peroxidation and boosts the antioxidant defense mechanism [58].

The activity of another piperine derivatives (Fig. 4i) (MAO-B, IC_{50} = 100 M) decreased as the number of carbon atoms in the ring increased. The elimination of N atom in other derivative (Fig. 4j) resulted in a modest increase in MAO-B inhibitory action. Because the nitrogen atom reduces the lipophilicity of the ring structure, it can be a role in increasing new derivative (Fig. 4k) affinity (MAOB: IC_{50} = 0.666 M), which is found to be more potent than compound (IC_{50} = 1.13 M for MAO-B) [59].

Another synthesized novel derivatives of piperine (Fig. 4l-m) obtained from *Piper nigrum* were screened for the potent antioxidant activity and these derivatives also have a capacity to reduce the risk factor for other various pathological diseases like cancer, diabetes mellitus, tumor, *etc*. [60].

Conclusion

Piperine obtained from black pepper have great potential as an antioxidant and used as a starting precursor for several reactions to produce various derivatives of piperine. The structure activity relationship and mechanism of action of piperine and its derivative as an antioxidant were also discussed in this article.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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