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A Comprehensive Review of Phytochemicals, Synthetic Strategies, and Bioactivities of *Piper nigrum* (Black Pepper)

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A Comprehensive Review of Phytochemicals, Synthetic Strategies, and Bioactivities of *Piper nigrum* (Black Pepper)

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Highlights

- Comprehensive review of phytochemicals and synthetic approaches of compounds from *Piper nigrum*, integrating classical and modern strategies.
- Valuable resource for researchers interested in the chemical, synthetic, and medicinal potential of *Piper nigrum*
- Identification of research gaps and future prospects for translating *Piper nigrum* compounds into therapeutic applications.

Abstract

Due to its rich array of bioactive compounds, black pepper (*Piper nigrum*) is not only a spice in kitchens worldwide, but a plant of significant medicinal interest as well. Among these, piperine has wide-ranging biological effects and has become a focal point in scientific research. Besides piperine, black pepper also contains numerous other phytochemicals, like essential oils, flavonoids, terpenes, and lignans-all of which have shown pharmacological activities. This review offers an in-depth look at the various phytochemicals found in black pepper, detailing both traditional and modern techniques used for their extraction and purification. Particular attention is given to the total synthesis and chemical modifications of piperine and related compounds, outlining major developments and methodologies in this area. The review also briefly touches on the therapeutic applications validated so far. Overall, this work is intended to be a valuable resource for researchers interested in the chemical, synthetic, and medicinal potential of *Piper nigrum.*

Keywords: *Piper nigrum*; phytochemicals; piperine; black pepper; king of spices; alkaloid

1. Introduction

Natural products have long served as invaluable resources in drug discovery, with over 60% of currently approved pharmaceuticals being derived from or inspired by natural compounds, particularly in therapeutic areas such as anti-infective, anticancer, and anti-inflammatory agents [1]. Among the numerous botanicals explored for bioactive secondary metabolites, *Piper nigrum* L., commonly known as black pepper, occupies a distinguished place due to its dual role as a culinary spice and a traditional medicinal agent [2].

Belonging to the Piperaceae family, *P. nigrum* is native to the Western Ghats of India and is now widely cultivated across tropical regions in Asia and other parts of the world [3,4]. Revered as the "King of Spices," black pepper has been an integral part of traditional medicine systems such as Ayurveda, Siddha, and Traditional Chinese Medicine. It has been employed for the treatment of various ailments, including gastrointestinal disturbances, respiratory disorders, and inflammatory conditions [5].

Phytochemically, *P. nigrum* is a rich source of diverse secondary metabolites, including alkaloids, amides, flavonoids, lignans, terpenes, and essential oils [6]. Among these, piperine (**1**) is

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the most prominent and bioactive alkaloid, responsible for the characteristic pungency of black pepper. It was first isolated in 1819 by Hans Christian Ørsted as 1-piperoylpiperidine. [7,8]

The structure of piperine was elucidated in 1850 [9], and its stereochemistry (*trans–trans* configuration) was later verified by Doebner and further by Ladenburg and Scholtz [9]. The crystal and molecular structure were later determined by Grynpas and Lindley [10].

Numerous scientific investigations have confirmed the versatile pharmacological activities of piperine, supporting its ethnomedicinal relevance since ancient times. These include antioxidant, anti-inflammatory, antimicrobial, anticancer, anticonvulsant, insecticidal, antidiabetic, and bioenhancer effects [11]. Other phytochemicals isolated from *P. nigrum*, such as chavicine, piperidine, β-caryophyllene, and limonene, have also shown significant bioactivity [12].

Dyer and colleagues have extensively reviewed the isolation, synthesis, and evolutionary ecology of piperamides, highlighting their ecological significance within the *Piper* genus [13]. Our previous review similarly underscored the wide-ranging pharmacological effects of black pepper, including its roles in obesity management, neuroprotection, antimicrobial resistance, and more [8]. In a notable study, Tezuka et al. reported the isolation of 19 distinct alkamides from *P. nigrum*, which exhibited inhibitory effects on the human liver microsomal enzyme CYP2D6 [14]. **Figure 1** summarizes some of the major phytochemicals identified in black pepper [15].

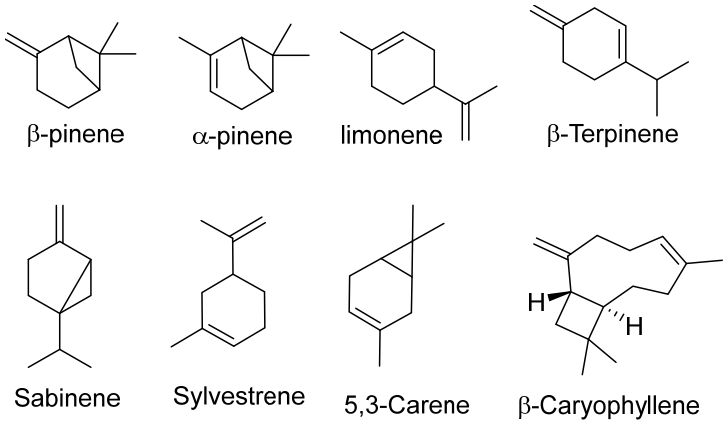

Figure 1. Chemical structures of predominant essential oil constituents from *Piper nigrum* [34].

Recent research has increasingly focused on the therapeutic versatility of piperine and its analogs across numerous disease models and pharmacological domains, such as: COVID-19 management [16,17], cardiovascular protection [18], synergistic use with cisplatin in apoptosis induction [19], electrochemical behavior [20], autoimmune encephalomyelitis modulation [21], ischemic stroke recovery [22], promotion of autophagic flux [23], c-myc gene regulation [24], hepatocellular carcinoma treatment [25], lipid metabolic improvement [26], anticancer nanoparticle development [27], breast cancer therapy [28], enhancement of drug bioavailability, e.g., domperidone [29], piperine-based urea analogs for cancer [30], neuroprotection in neurological disorders [31].

While multiple reviews have discussed the pharmacological and ethnobotanical relevance of *P. nigrum*, there is still a space of literature focusing specifically on the isolation techniques, synthetic strategies, and bioactivity assessments of its core phytochemicals—particularly piperine and its derivatives. As synthetic organic chemistry continues to evolve, understanding structure-activity relationships (SAR) and developing more potent, stable, and bioavailable piperine analogs is of growing interest [32].

Therefore, this review aims to present a comprehensive and up-to-date overview of the phytochemicals derived from *P. nigrum*, with an emphasis on the isolation techniques, synthetic approaches, and bioactivity assessments of its major constituents-particularly piperine. By integrating perspectives from natural product chemistry, medicinal chemistry, and pharmacognosy,

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this work seeks to highlight both classical foundations and recent advancements, thereby providing a valuable reference for researchers exploring the therapeutic potential and chemical innovation surrounding black pepper phytochemicals.

2. Botanical Description of Black Pepper

Black pepper (*Piper nigrum L.*), a member of the Piperaceae family, is a perennial woody vine known for its climbing habit, typically reaching up to 10 meters in height with support. Cytogenetically, it is a balanced tetraploid species (2n = 52), though no diploid relatives (2n = 26) have been reported in India [33,34]. Based on morphological and biosystematic analyses, *P. wightii*, *P. trichostachyon*, and *P. galeatum* are believed to be its ancestral species. The plant features dimorphic branching, with monopodial orthotropic (upright) branches for growth and sympodial plagiotropic (horizontal) branches for fruiting. Adventitious roots develop from the base of mature stems and from each node on the orthotropic shoots, aiding in climbing. The leaves are simple, alternate, and borne on grooved petioles (2-5 cm long), with variable blade sizes ranging from 8-20 cm in length and 4-12 cm in width. In Indian conditions, flowering typically begins 2-3 years after planting, aligning with the May-July monsoon [34]. The pendulous inflorescences, or spikes, emerge opposite the leaves on fruiting branches, range from 3-15 cm long, and bear flowers that bloom within 6-10 days of spike emergence. While wild varieties are generally dioecious, cultivated forms are mostly monoecious and primarily self-pollinate, though protogyny (female organs maturing before male) is also observed. The mature fruits are spherical drupes (~5 mm in diameter) that are harvested and sun-dried for use [34,35].

3. Chemical Composition and Major Classes of Compounds in Piper nigrum

P. nigrum is a rich source of nutrients and bioactive phytochemicals that contribute to its characteristic pungency, aroma, therapeutic properties, and nutritional value. Its chemical composition can be broadly categorized into nutritional components and major classes of secondary metabolites. **Table 1** highlights nutritional composition and **Table 2** highlights essential oils from *P. nigrum.* Similarly **Figure 1** shows structure of major essential oils and **Figure 2** shows major secondary bioactive metabolites from *P. nigrum*.

A. Nutritional Composition

Black pepper seeds are nutritionally dense. Per 100 grams, they provide approximately 66.5 g of carbohydrates, 10 g of protein, and 10.2 g of fat. The spice is also abundant in essential minerals, including potassium (1200 mg), calcium (400 mg), magnesium (235.8-249.8 mg), and phosphorus (160 mg), along with smaller amounts of sodium, iron, and zinc. These elements play vital roles in human physiological functions [34,36].

In terms of vitamins, black pepper contains appreciable levels of vitamin C and B-complex vitamins such as B1 (thiamine), B2 (riboflavin), and B3 (niacin), which contribute to metabolic and immune support [34,37].

Additionally, black pepper contains polyphenolic compounds, including tannins (2.11-2.80 mg/100 g), flavonoids like catechin, quercetin, and myricetin, as well as carotenoids such as lutein and β-carotene. These compounds exhibit potent antioxidant and anti-inflammatory activities [34].

Table 1. Nutritional composition of 100 g of black pepper [34,36,38–40].

Chemical Composition	Concentration
Proximate	
Energy (Kcal)	400.0
Carbohydrate (g)	66.5
Fat (g)	10.2
Protein (g)	10.0
Total Ash (%)	3.43-5.09

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Water (g)	8.0
Crude Fibre (%)	10.79-18.60
Minerals	
Calcium (mg)	400.0
Magnesium (mg)	235.8-249.8
Potassium (mg)	1200.0
Sodium (mg)	10.0
Phosphorus (mg)	160.0
Iron (mg)	17.0
Zinc (mg)	1.45-1.72
Vitamins	
Vitamin C (mg)	27.46-32.53
Vitamin B1 (mg)	0.74-0.91
Vitamin B2 (mg)	0.48-0.61
Vitamin B3 (mg)	0.63-0.78
Metabolites	
Tannin (mg)	2.11-2.80
Flavonoids	
Catechin (µg)	410.0
Myricetin (µg)	56.0
Quercetin (µg)	13.0
Carotenoids	
Lutein (µg)	260.0
β-Carotene (µg)	150.0

B. Bioactive Secondary Metabolites

Alkaloids: The principal alkaloid in black pepper is piperine, which is primarily responsible for its pungency and a wide range of biological effects, including antioxidant, anti-inflammatory, and bioenhancing properties. Piperine content in seeds ranges from 2.13% to 5.80% [34]. Many alkamides found in P. nigrum are discussed by Guo and coworkers in their review article published in 2025 [41].

Essential Oils (EOs): Black pepper essential oils are composed of a complex mixture of volatile compounds, predominantly monoterpenes and sesquiterpenes. The EO yield varies depending on the plant part and extraction method-ranging from 1.24-5.06% in berries and 0.15-0.35% in leaves [42–44]. Major constituents include β-caryophyllene, α-pinene, limonene, sabinene, and nerolidol, though regional variations exist. Minor EO components include β-elemene, δ-elemene, α-zingiberene, and others in trace amounts. Chemical constituents of essential oils of P. nigrum from seed is discussed in details by Asadi [45].

Oleoresins: Oleoresins represent a concentrated extract of both volatile and non-volatile compounds. Their content ranges from 4.27% to 12.73% across different cultivars and conditions. These extracts are highly valued in the food and pharmaceutical industries for their intense flavor and therapeutic potential [34,39].

Phenolic Compounds: Black pepper is enriched with flavonoids (e.g., catechin, quercetin, myricetin) and carotenoids (e.g., lutein, β-carotene), which function as antioxidants and exhibit various health-promoting effects, including cardiovascular and neuroprotective benefits [34].

Amides: In addition to piperine, black pepper contains a range of amide compounds that share structural similarities and contribute to both the pungency and bioactivity of the spice [34].

Steroids and Triterpenoids: Although present in smaller quantities, these compounds may exert beneficial pharmacological actions, including anti-inflammatory and immunomodulatory effects [34].

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Table 2. Composition range of major essential oil constituents of *Piper nigrum* from various origins [34,39,44,46–49].

Constituent	Concentration Range (%)
β-Caryophyllene	2.09–26.95
Limonene	15.13–29.90
Sabinene	0.00–19.23
α-Pinene	3.88–20.86
β-Pinene	12.1–19.0
δ-3-Carene	9.23–55.43
β-Bisabolene	1.32–7.96
α-Humulene	1.11–2.44
α-Copaene	0.20–5.51
α-Cadinol	0.18–4.89
α-Thujene	0.60–2.94
Nerolidol	0.14–66.32
β-Phellandrene	3.16–4.80
Myrcene (β-Myrcene)	1.99–2.9
1-Napthalenol	3.00
Sylvestrene	10.67
Germacrene D	2.17
Isoterpinolene	1.40
Linalool	2.10
β-Terpenine	19.50
α-Phellandrene	2.20

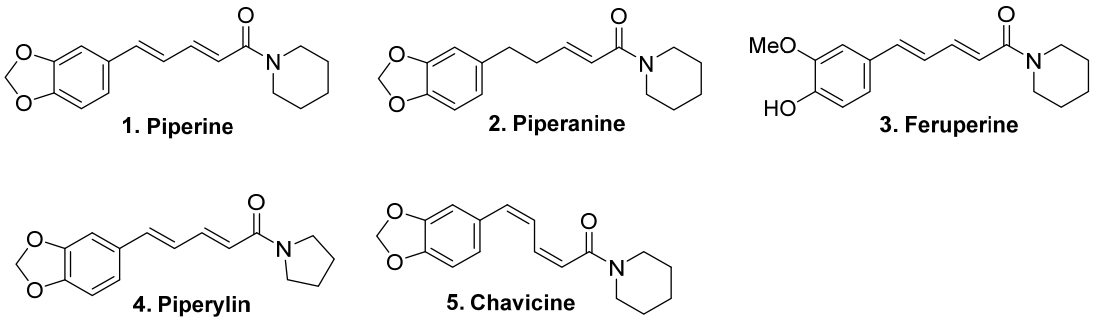

Figure 2. Some of the compounds isolated from *Piper nigrum.*

Piperine: Piperine is the principal alkaloid in *Piper nigrum*, accounting for 2–9% of the fruit's weight. [6] It is responsible for the pungency of black pepper and exhibits a range of biological activities, including: enhancement of nutrient and drug bioavailability [50], anti-inflammatory and antioxidant effects [51], neuroprotective and antimicrobial properties [52].

Chavicine: Chavicine is an isomer of piperine formed during processing. While structurally similar, chavicine lacks pungency and is less stable, often reverting to piperine under heat or light exposure. It contributes to the variability in pepper's pungency based on storage and processing [53,54].

Essential Oils: Essential oils constitute 0.4-7% of black pepper [6] and include: **m**onoterpenes: α-pinene, β-pinene, limonene [55]; sesquiterpenes: β-caryophyllene, caryophyllene oxide [56]. These volatiles are chiefly responsible for the aroma of black pepper and have antimicrobial and antioxidant effects.

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4. Extraction and Isolation Techniques of Phytochemicals from Piper nigrum

The extraction and isolation of phytochemicals from *P. nigrum* can be viewed in conventional solvent-based methods to advanced green technologies that enhance yield, purity, and sustainability [34]. Traditional extraction methods (TEM) are widely used due to their simplicity, cost-effectiveness, and historical reliability. However, they often involve long extraction times, large solvent volumes, and potential degradation of heat-sensitive compounds [57–61]. Modern methods aim to improve extraction efficiency, reduce solvent usage, and preserve bioactivity. These are more eco-friendly and are suitable for industrial-scale applications [61–65]. Below **Table 3** list some TEM and MGET.

Table 3. Different Extraction and Isolation Techniques of Phytochemicals from P. nigrum.

Category	Extraction Method	Technique/Process	Target Compounds	Advantages	Limitations
Traditional Extraction Methods (TEM)	**Solvent Extraction**	Maceration or Soxhlet with ethanol, methanol, acetone, chloroform, hexane	Piperine, essential oils, alkaloids	Simple, widely used, low cost	Low selectivity, solvent residues, degradation of thermolabile compounds
	Steam Distillation	Steam passed through crushed pepper to vaporize volatiles	Essential oils	Effective for volatile oils, easy setup	High temperature may degrade sensitive compounds
	Cold Pressing / Infusion	Mechanical pressing or soaking in oil	Flavor compounds, minor volatiles	Traditional, non-toxic, culinary use	Low efficiency, not suitable for alkaloid extraction
Modern & Green Extraction Techniques (MGET)	**Supercritical Fluid Extraction (SFE)**	Supercritical CO_2 (often with ethanol)	Piperine, essential oils	High purity, non-toxic, tunable selectivity	Expensive equipment, technical complexity
	Ultrasound-Assisted Extraction (UAE)	Ultrasonic waves enhance solvent penetration	Piperine, phenolics	Fast, solvent-saving, good for heat-sensitive compounds	Scale-up limitations, equipment cost
	Microwave-Assisted Extraction (MAE)	Microwave energy heats plant-solvent matrix	Piperine, flavonoids, polyphenols	High efficiency, less solvent, reduced time	Risk of thermal degradation if not optimized
	Pressurized Liquid Extraction (PLE)	High pressure and temperature solvent-based extraction	Polar and non-polar compounds	Rapid, efficient, minimal degradation	Requires specialized apparatus
	Enzyme-Assisted Extraction (EAE)	Enzymatic treatment (e.g., cellulase, pectinase)	Phenolics, alkaloids	Mild, eco-friendly, suitable for food-grade products	Enzyme cost, need for process optimization

5. Chromatographic and Spectroscopic Identification Methods

To identify and analyze the phytochemicals in *P. nigrum*, a variety of chromatographic and spectroscopic techniques are employed. High-Performance Liquid Chromatography (HPLC) is commonly used for the separation and quantification of compounds like piperine, while Gas Chromatography (GC) is preferred for analyzing essential oils. Thin-Layer Chromatography (TLC)

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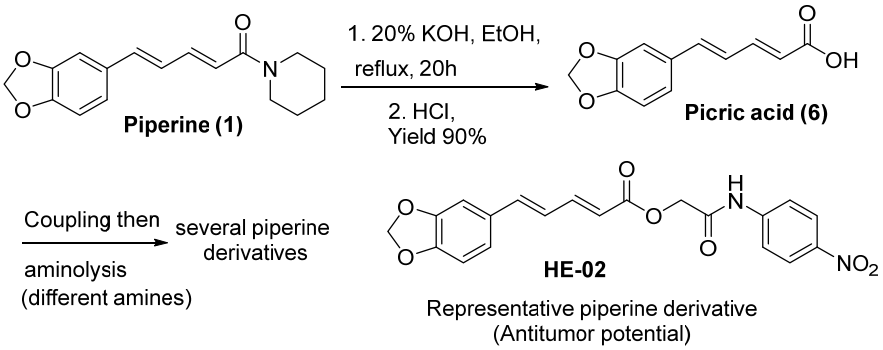
offers a simple and cost-effective method for preliminary analysis, and Flash Chromatography allows for efficient large-scale isolation of target compounds. Spectroscopic methods like UV-Vis Spectroscopy are frequently used for the quantification of piperine, while Fourier Transform Infrared Spectroscopy (FTIR) helps in identifying functional groups within the compounds. Nuclear Magnetic Resonance (NMR) Spectroscopy provides detailed structural information, making it invaluable for structural elucidation of complex compounds. Mass Spectrometry (MS), often coupled with GC-MS or HPLC-MS, provides accurate molecular identification and quantification, particularly for volatile and alkaloid compounds. Finally, Raman Spectroscopy offers a non-destructive approach for molecular identification through vibrational analysis. These combined methods enable precise characterization of bioactive compounds, ensuring comprehensive analysis of black pepper's phytochemical profile [57,66–70].

6. Synthetic and Semi-Synthetic Approaches for Compounds from Piper nigrum

P.nigrum is a rich source of bioactive compounds, particularly piperine, which is the primary alkaloid responsible for its characteristic pungency. While the extraction of these compounds from natural sources remains common, synthetic and semi-synthetic methods have gained prominence in recent years due to their efficiency, scalability, and ability to produce modified derivatives with enhanced properties. The following sections explore the synthetic approaches to the major compounds from black pepper, including the challenges and advances in their synthesis.

6.1. Isolation of Piperine from Natural Sources and Amide Hydrolysis

Initially, piperine (**1**) was isolated from natural sources such as black and white *P. nigr*um. It was then subjected to alkaline hydrolysis to yield piperic acid (**6**), which served as a key intermediate for synthesizing various amide derivatives for biological studies, as shown in **Scheme 1** [71–73]. However, due to the increasing demand for piperine, its natural supply has become insufficient for large-scale applications. This limitation has driven the development of synthetic routes to produce piperine and its analogs more efficiently. These synthetic approaches also enable structural modifications at the amide group, alkyl chain, and piperonal moiety to facilitate structure-activity relationship (SAR) studies.



Scheme 1. Hydrolysis of piperine and further derivatization.

For the first time, synthesis of piperine (**1**) was reported by Rtigheimer in 1882 [13,74], where piperidine react with acyl chloride derived from piperic acid (**6**) via hydrolytic cleavage of the isolated natural piperine. Only after 12 years later in 1894, Ladenburg and Scholtz isolated other additional chemical components from piper and also the structure elucidated via hydrolysis and total synthesis [74,75]. In 1950 Spring and Stark reported the isolation, identification, and synthesis of piperttine from *Piper nigrum* [76].

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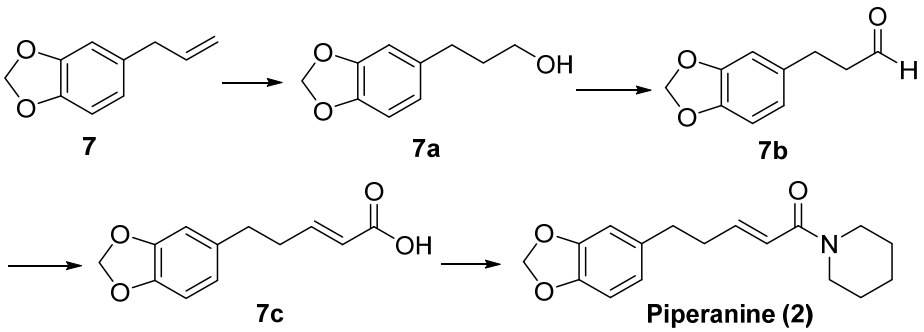
6.2. Isolation and Structure Elucidation of Piperanine

In 1971 James reports isolation, structure elucidation by the synthesis of piperanin (**scheme 2**) [77], and reports the *trans* geometry. Safrole (**7**) converted to 3-(3,4-methylenedioxyphenyl)propanol (**7a**) by hydroboration with diborane then alkali hydrogen peroxide treatment. Then (**7a**) dissolved in DMSO and reacted with anhydrous phosphoric acid then finally added freshly distilled dicyclohexylcarbodiimide to affords 3-(3,4-Methylenedioxyphenyl)propionaldehyde (**7b**). Carboethoxymethylenetriphenylphosphorane in benzene added to afford acid (**7c**) which reacted with oxalyl chloride in benzene and added piperidine to afford piperanine(**2**).



Scheme 2. Piperanine synthesis by James T. Traxler in 1971.

6.3. Isolation and Synthesis of Pipericide and Dihydropipericide from Piper nigrum

In 1979, two insecticidal amides; pipericide (**8**) and dihydropipericide **(8a)** were isolated from *P. nigrum* by Miyakado and Yoshioka [78–80]. Synthesis of both the pipericide and dihydropipericide is reported by Rotherham and Semple in 1998 **(scheme 3)** [81]. The coumaperine, *N*-trans-feruloyl tyramine, *N*-trans-feruloyl piperidine, (4-hydroxy-3-methoxyphenyl)-2E, *4E*-pentadienoyl piperidine, and 3-methoxyphenyl)-*2E*-pentenoyl piperidine are isolated from *P. nigrum* in 1980 by Nakatani and coworkers [82], and the structure and synthesis of new Phenolic amides from *P. nigrum* reported in 1981 by Inatani coworkers [83].

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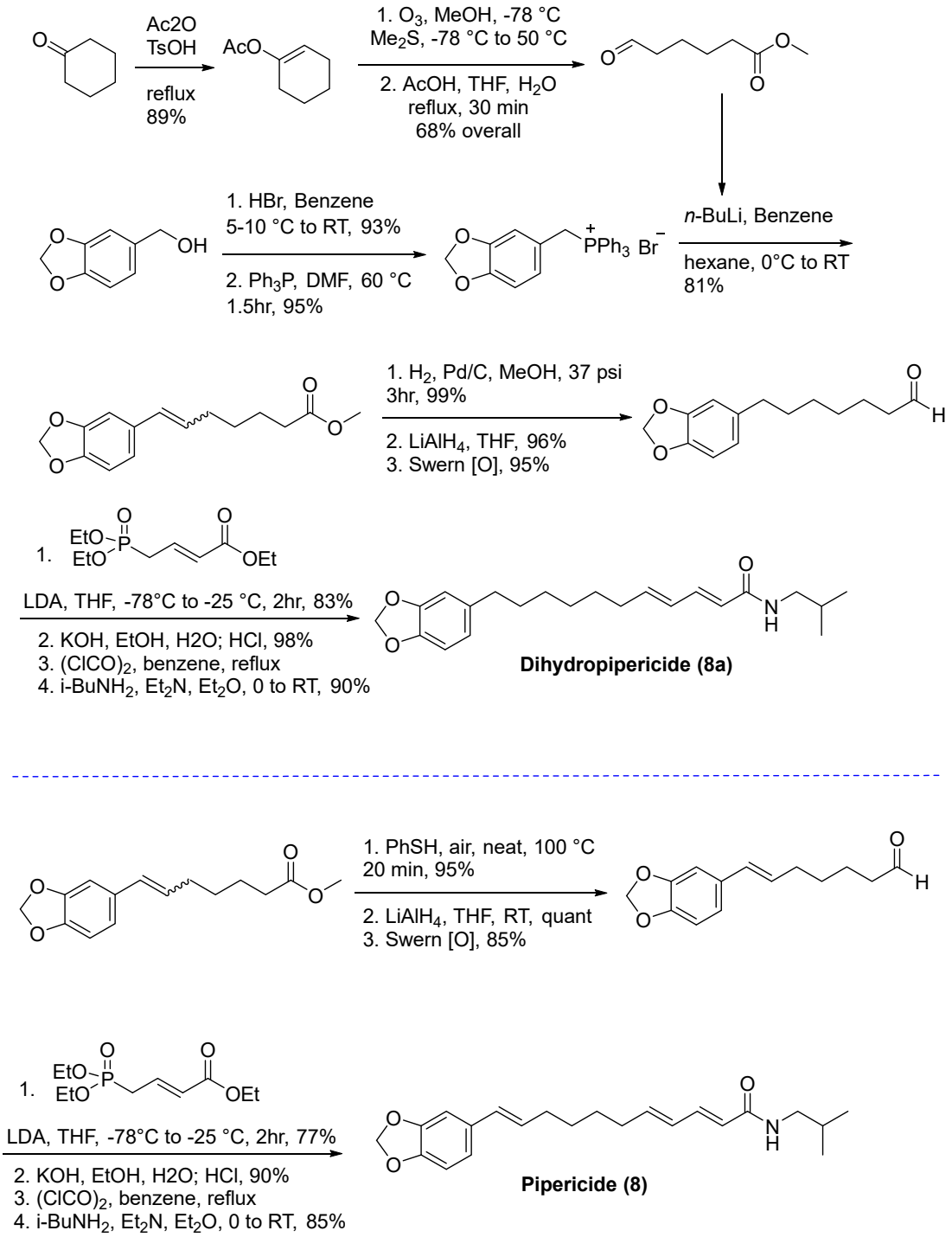

Scheme 3. Synthesis of Pipericide and Dihydropipericide.

6.4. Synthesis of Piperine from piperonaldehyde

In 1979 Tsuboi and Takeda co-work described three-step synthesis of piperine (**scheme 4**) from commercially available piperonal aldehyde. The acetylene solution treated with piperonal in presence of potassium hydroxide at low temperature (-40 °C) to get propargylic alcohol (**9**) in good yield; then allowed thermal condensation with the *N*-acetylpiperidine diethyl-acetal to achieve intermediate **10**, which undergo (3,3)-sigmatropic rearrangement to give allene amide **(11)**, then under base (^{t}BuOK) furnish a mixture of Isochavicine and Piperine (**1**) in the ratio of 35:65 with 86% yield [84].

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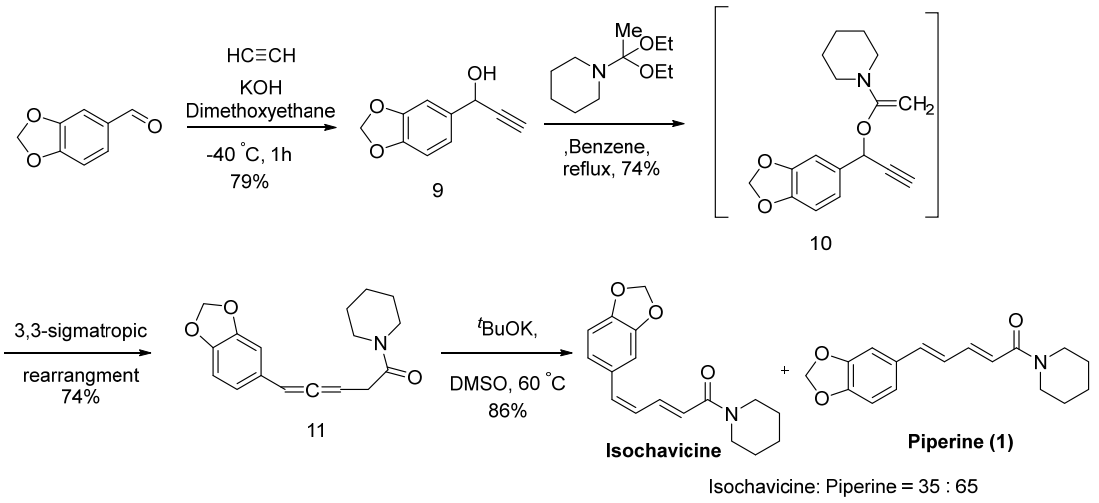
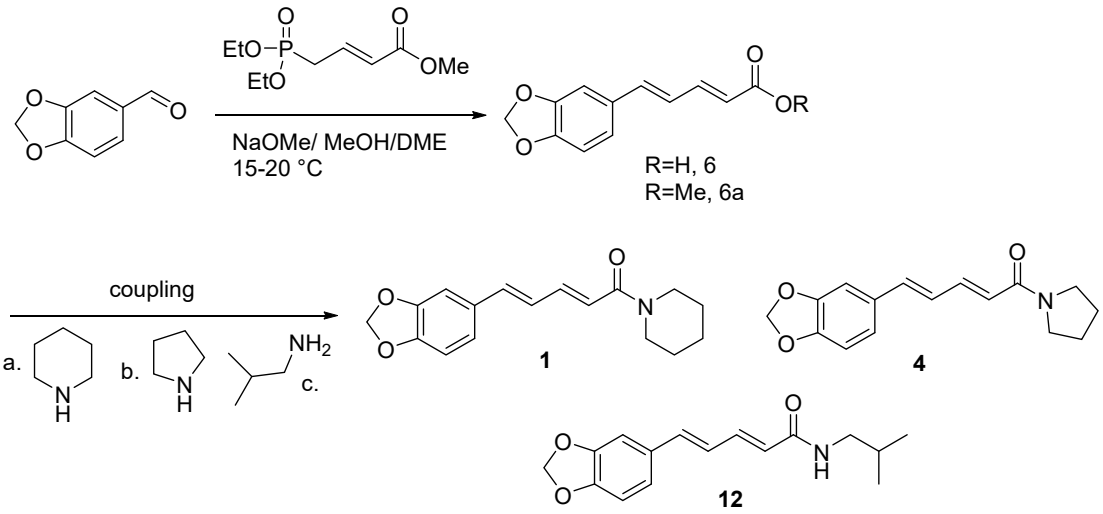


Scheme 4. Tsuboi and Tekeda method of synthesis for piperine in 1979.

6.5. Stereoselective Synthesis of Piperine and Related Pepper-Derived alkaloids

Some earlier syntheses by Feugeas, 1964; Lurik et al., 1971; Dallacker and Schubert, 1975 have suffered from low yield even after several steps [85] having stereoselectivity issue (Tsuboi and Takeda, 1979), so in 1981 Olsen and Spessard reports two steps stereoselective synthesis of piperine and its related pepper alkaloids (**Scheme 5**). Where piperonal first treated with the ylide made from diethylphosphono-butenoate to afford methyl piperate (**6a**) then hydrolysis giving piperic acid (**6**) and subsequent coupling giving various amides; piperine (**1**), Trichostachine (or also known as Piperylin) (**4**), Piperlonguminine (**12**) [73].



Scheme 5. Stereoselective Synthesis of Piperine and Related Pepper-derived alkaloids by Olsen and Spessard in 1981.

6.6. Stereoselective Synthesis of Piperine via a Double Elimination Reaction

In 1986 Mandai and coworkers reported two steps highly stereoselective synthesis of piperine via a double elimination reaction of a beta-acetoxy sulphone (**scheme 6**) [86]. Here they prepared sulphone (**13**) substrate from piperonal and couple with an aldehyde (**14**) by using a strong base (*n*-BuLi) to get acetate (**15**) then treating with *t*-BuOK gives piperine (**1**) in good yield (77%) with stereocontrol of 90% ee.

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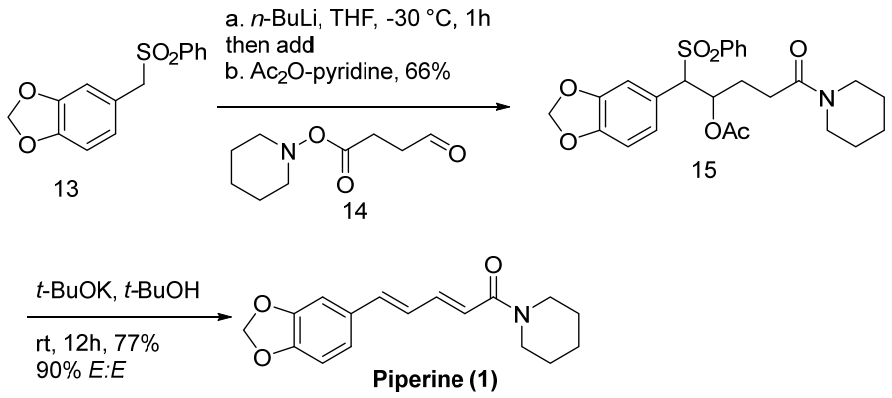
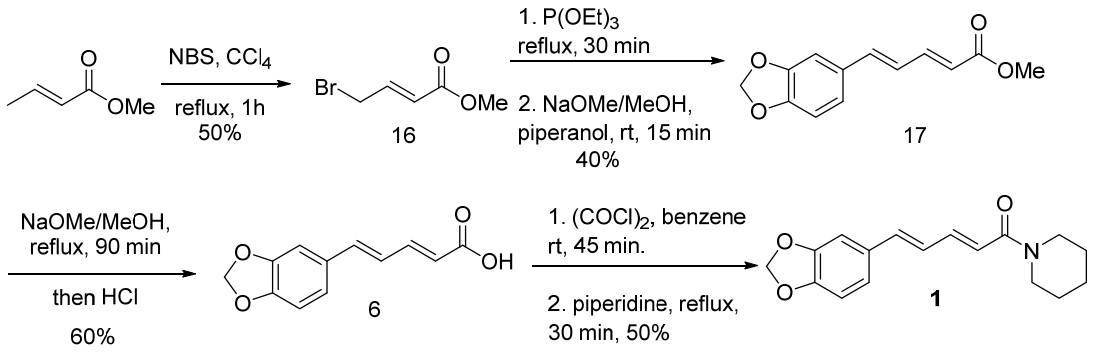


Scheme 6. Mandai and coworkers synthesis of piperine in 1986.

6.7. Other Piperine Synthesis Methods

In the year 1995, Sloop reported a synthetic strategy for piperine (**scheme 7**) and carpanone [87]. The allylic bromination of the methyl crotonate by treating with NBS (*N*-bromosuccinamide) and carbon tetrachloride under reflux giving moderate yield (**16**); which is now available commercially. Then via aldol condensation gives methyl piperate (**17**), which then undergo ester hydrolysis to afford acid (**6**) and activation of acid, then aminolysis by piperidine gave piperine (**1**) with moderate yield (50%).



Scheme 7. Sloop strategy for synthesisi of piperine in 1995.

Strunz and Findlay (in 1994 and 1996) reported a Sakai aldol condensation-Grob fragmentation pattern to incorporate unsaturation stereospecifically for the synthesis of several piper amides retrofractamide A (**18**), pipericide (**8**), piperolein A (**19**), *piperamide-C9:3(2E,4E,8E)*(**20**) *and* piperstachine (**21**), based on piperonyl framework in same work they also report the synthesis of six nonaromatic piper (**scheme 8**) [88,89].

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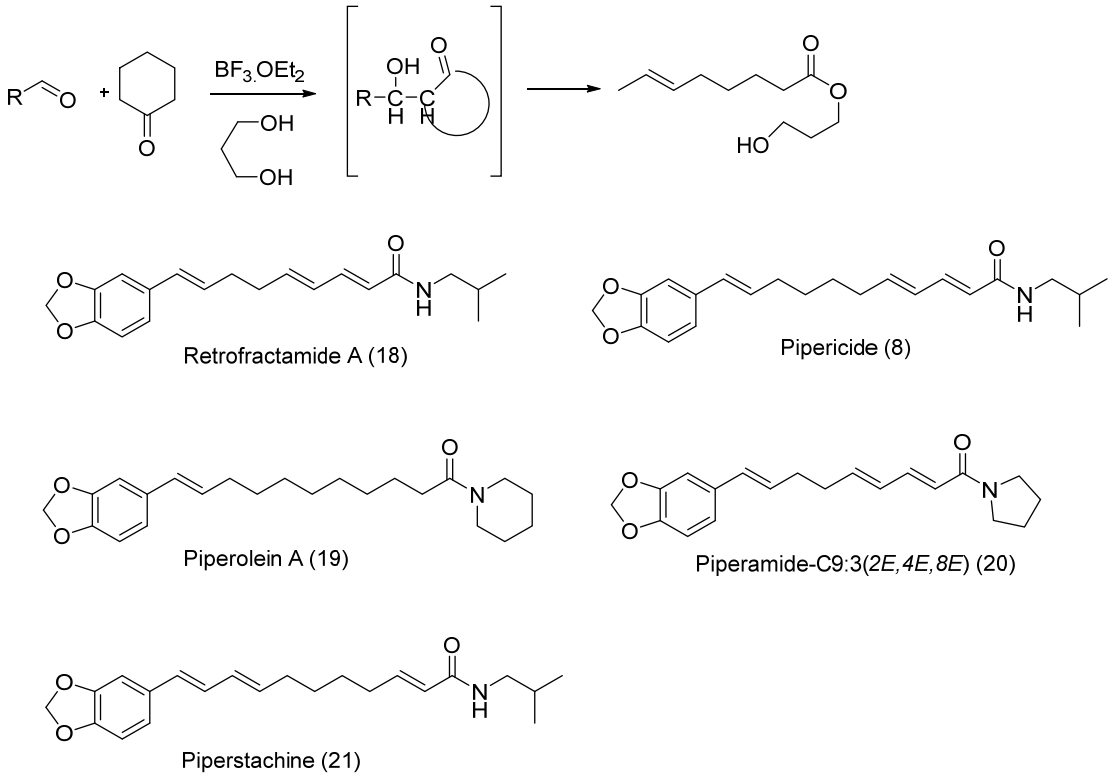
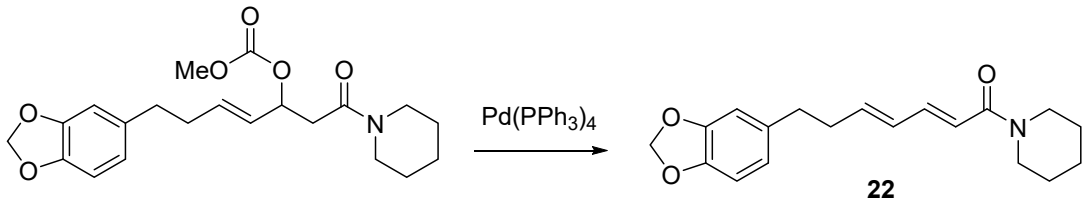


Scheme 8. Use of Sakai aldol condensation-grob fragmentation for synthesis of several piper amides by Strunz and Findlay (in 1994 and 1996).

In 1999, a palladium-catalyzed alkenylation reported by Schwarz and Braun for the synthesis of piperdardine (**22**) (**scheme 9**) [90].



Scheme 9. Synthesis of piperdardine (22) via palladium catalyzed alkenylation in 1999.

In the year 2000 total synthesis of piperine and its analogs were carried out by Chandrasekhar and coworkers (**Scheme 10**) [91]. The commercially available furfural converted to its hydrazine (**23**) which then treated with Grignard reagent, benzodioxole-MgBr (**24**) in dry THF to afford (*2E,4E*)-5-(benzo [*d*] [1,3]dioxol-5-yl)penta-2,4-dienal (**25**) then converted to piperic acid (**6**) via Pennick oxidation and coupled with DCC and amine hydrolysis gives different amides; piperine (**1**) and other congeners piperylin (**4**) and Piperlonguminine (**15**).

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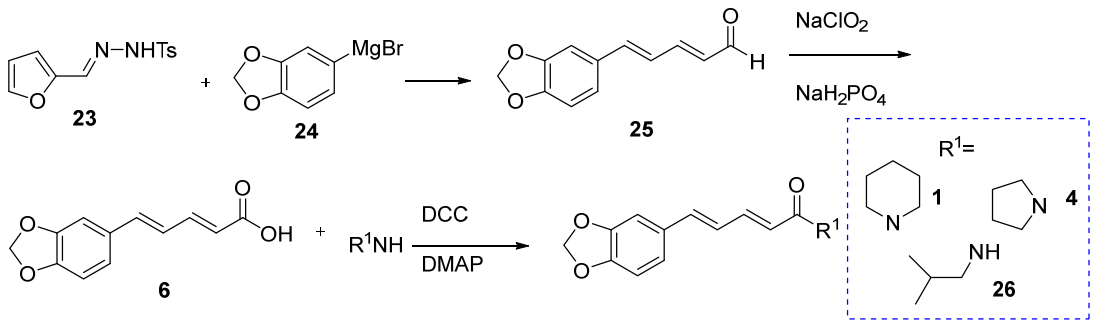
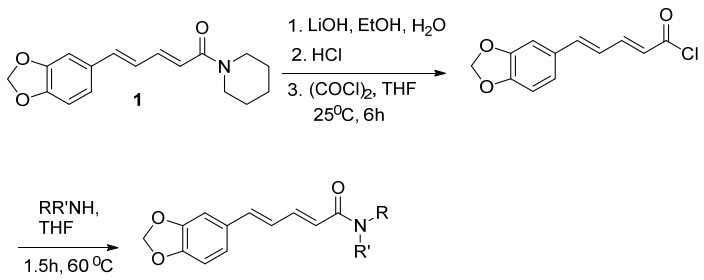


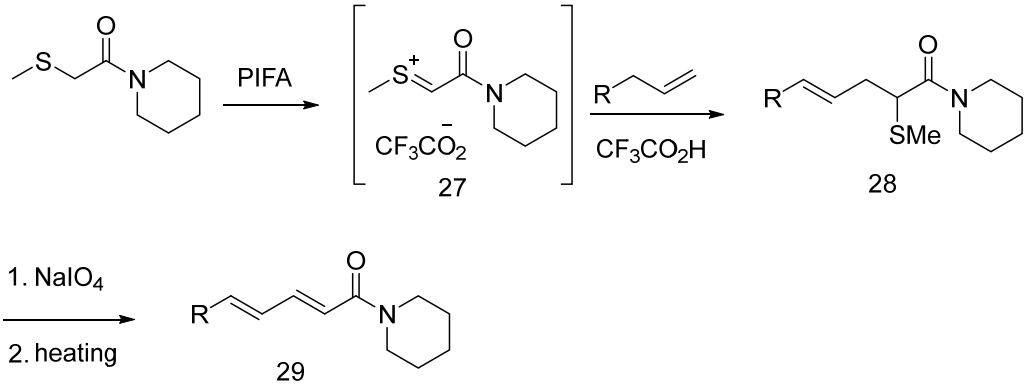
Scheme 10. Total synthesis of piperine and its analogs by Chandrasekhar and coworkers in 2000.

In 2000 Paula and coworkers synthesized a piperine derivatives (scheme 11a) and tested the insecticidal activity against Brazilian insects (*Ascia monuste orseis, Acanthoscelides obtectus, Brevicoryne brassicae, Protopolybia exigua and Cornitermes cumulans*). Where they isolated the piperine and piperiline from *P. nigrum*, then hydrolyzed it to piperic acid and synthesized the 16 different new amide [92]. The result shows the mortality of insects ranges from 0 to 97.5% varied on the compound and the insect species.



Scheme 11. Synthesis and insecticidal activity of new amide derivatives of piperine.

Kang and coworkers used hypervalent iodine (III) for generating a pummerer-type reaction in 2001 [93]. The generated reactive intermediate (**27**) then undergo ene type reaction to form a olefin type moiety (**28**) which under heating in presence of hypervalent iodine affords dieneamides (**29**) as depicted in **scheme 12.**



Scheme 12. Synthesis of dieneamides by Kang and coworkers in 2001.

In 2001, Schobert and coworkers reported the synthesis of piperine via intramolecular three-component reaction between the aldehyde, ketenylidenetriphenylphosphorane, and amines (**scheme 13**). [73] First the commercially available piperanol converted to corresponding alfa-beta-unsaturated aldehyde (**30**) by 2 steps: the first generation of *cis-trans*-isomeric mixtures of 3,4-(methylenedioxy)-

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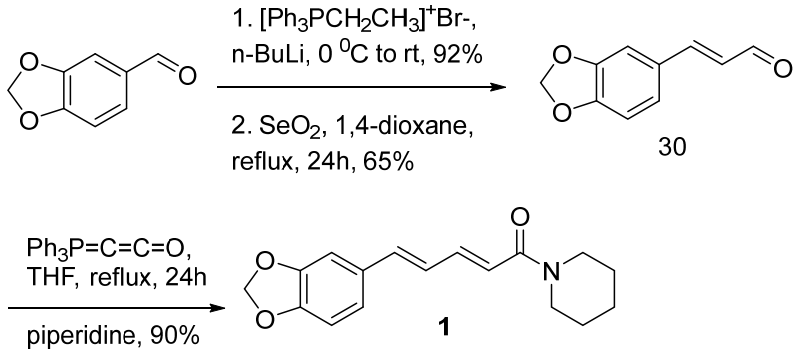
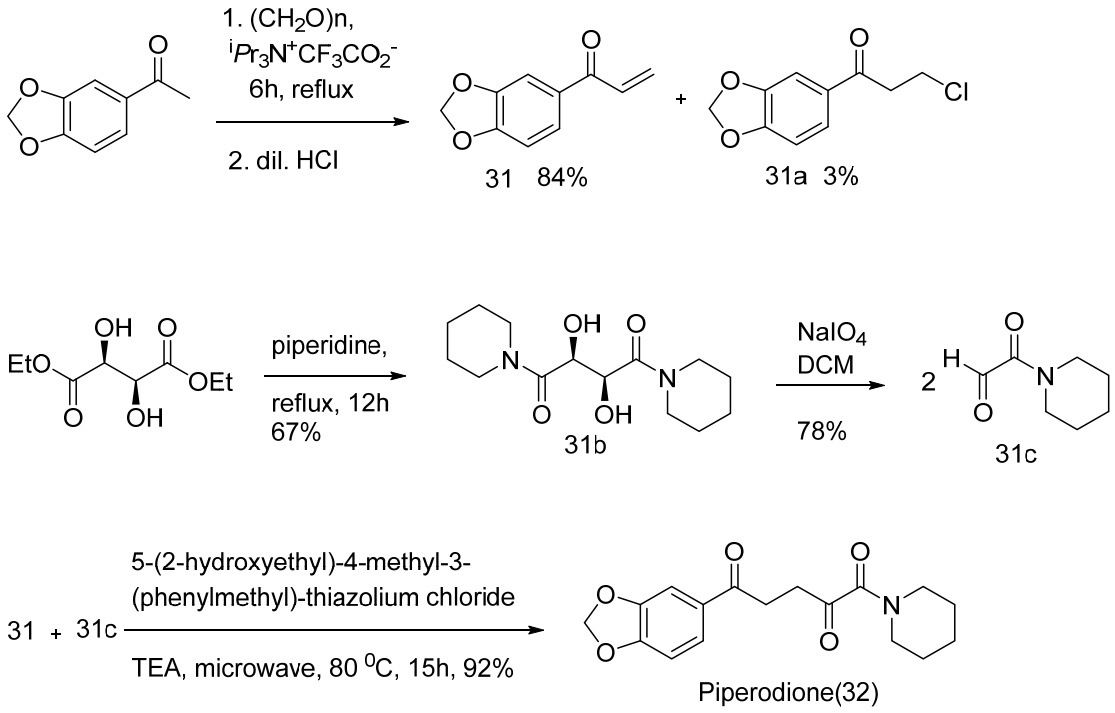
b-methylstyrene via olefination with ethylidenetriphenylphosphorane and then selenium dioxide mediated trans-selective allylic oxidation to give *E*-aldehyde (**30**) which then undergo three-component domino reaction with the available ketene (Ph3P=C=C=O) and piperidine to obtain desired piperine (**1**) in good yield (90%).



Scheme 13. Schobert and coworkers synthesis of piperine (**1**) in 2001.

In 2014 Rene Csuk and coworkers reported first-time total synthesis of piperodione (**32**) and two other analogs having cyclopentane and azitidine amine rings. [94] As shown in **scheme 14**; the commercially available dioxyacetophenone allowed Mannich reaction followed by acidic workup afford propanone (**31**) along with side product **31a**. The commercially available diethyl tartrate treated with piperidine under reflux to afford diamide (**31b**) which undergoes cleavage by silicagel supported $NaIO_4$ to form an aldehyde(**31c**) which then treated with propanone (**31**) to get the piperodione (**32**). [94]



Scheme 14. First total synthesis of piperodione by Csuk and coworkers in 2014.

In 2015, Mihovilovic and coworkers reported the synthesis of piperine analogs via Heck cross-coupling reaction of the conjugated dienamides allowing the rapid assembly of piperine derivatives

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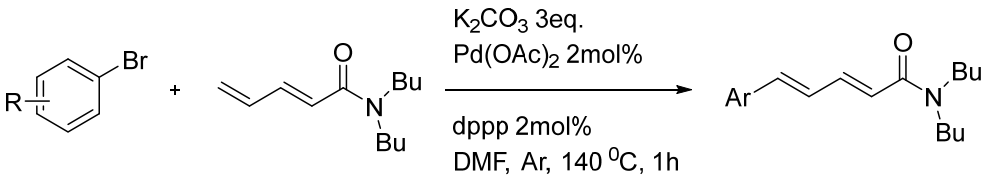
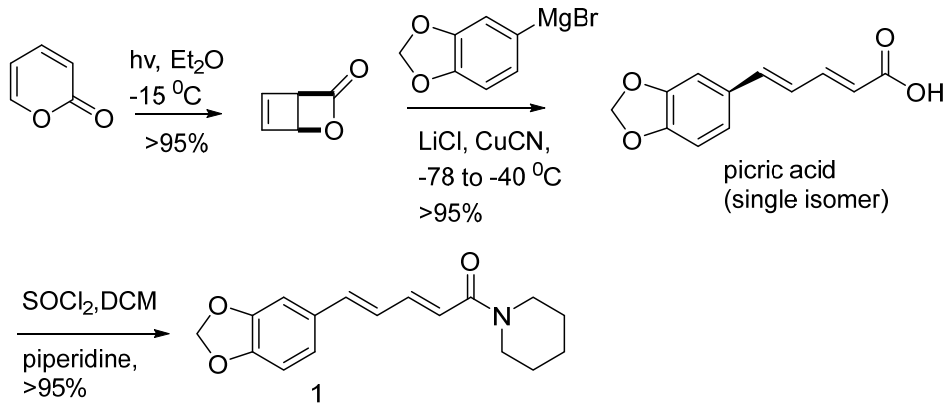
(15 compounds) with modified aromatic core (**scheme 15**). [95]. And the biological testing shows high efficacy and selectivity for $GABA_A$ or TRPV1 receptors.



Scheme 15. Synthesis of piperine analogs via Heck-coupling of conjugated dienes by Mihovilovic and coworkers in 2015.

In 2018, Bauer and coworkers presented a short and stereoselective, efficient synthetic pathway for piperine and its analogs (**Scheme 16**). [96] Here the in-situ generated cuprate undergoes a nucleophilic attack to the cyclobutene lactone. Then the newly formed aryl-substituted cyclobutene naturally undergoes conrotatory 4-pie-electrocyclic ring opening to give a single diastereomer, 4-arylpentadienoic acid which after activation can easily undergo amide hydrolysis to give piperine and various analogs.



Scheme 16. Three steps synthesis of piperine by Bauer and coworkers in 2018.

7. Bioactivity of Black Pepper and Isolated Phytochemicals

There are several review articles are published highlighting bioactivity of *P. nigrum* [6,15,18,97–102]. Most of the reported bioactivity are antioxidant [103], antibacterial, antimicrobial [103], hepatoprotective, anti-inflammatory, antifertility, antidepressant, antidiabetic, anticancer [104], antihyperglycemic [102]. Similarly the new phytochemicals identification study is also going on. Work purblished in 2023 by Luis and coworkers have done characterization and isolation of 26 different piperamides from *P. nigrum* [105].

8. Conclusions

Piper nigrum (black pepper) stands out as one of the most important medicinal spices, not only for its culinary value but also for its wide range of phytochemicals and therapeutic potential. This review consolidates extensive data on its nutritional content, essential oils, and diverse classes of secondary metabolites, particularly focusing on piperine-a principal alkaloid with notable pharmacological effects. Traditional and modern extraction techniques have been critically compared, emphasizing the shift toward eco-friendly and high-efficiency methods such as supercritical fluid extraction and ultrasound-assisted extraction. These techniques are instrumental

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in preserving the bioactivity of thermolabile constituents and facilitating industrial applications. Significant progress has also been highlighted in the total synthesis and structural modification of piperine and its analogs. Despite the extensive pharmacological evaluations, further research is warranted to translate these findings into clinical applications. Future studies should emphasize in vivo models, toxicological safety, formulation development, and clinical trials to fully harness the therapeutic potential of *P. nigrum* and its derivatives.

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Use of Artificial Intelligence: The authors declare that the content of this manuscript was developed entirely through original human effort and scholarly work. No generative artificial intelligence (AI) tools or automated writing technologies were used at any stage in the preparation, writing, or editing of this manuscript.

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