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Review

Mentha arvensis and *Mentha* × *piperita*-Vital Herbs with Myriads of Pharmaceutical Benefits

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Abstract: *Mentha arvensis* L. and *Mentha* × *piperita* L. are herbal plants belonging to the Lamiaceae family and are widely cultivated for their essential oils and culinary uses. These herbs are commercially valuable mints used in the preparation of herbal formulations, cosmetics, pharmaceuticals, and in food industries. Due to the presence of potential secondary metabolites, mints were employed to treat various disorders since ancient times in traditional medicines. The extracts of *M. arvensis* and *M.* × *piperita* can improve the function of digestive system, central nervous system and respiratory system of the human body. Majority of the health benefits of these herbs are attributed by the essential oil components. In addition, the administration of *M. arvensis* and *M.* × *piperita* under various pathological conditions studied in vitro and in vivo facilitated the recovery of detrimental ailments. Due to the increasing demand for natural product-based medicines, research is focused on the utilization of phytochemicals to treat various ailments. In order to provide a comprehensive overview of health benefits of *M. arvensis* and *M.* × *piperita*, the present endeavor deals with the antioxidant property, anti-inflammatory property, anti-microbial, and anti-cancer activities of both species. However, a deeper knowledge on the specific metabolites of *M. arvensis* and *M.* × *piperita* and their mode of action against different disease targets will accelerate the discovery of novel natural drugs with less side effects and higher efficiency.

Keywords: *Mentha*; essential oil; pharmaceutical benefits; natural drugs

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1. Introduction

Plants are viable reservoirs of phytochemicals with diverse medicinal values which form the vital ingredients for various pharmaceutical and herbal formulations [1]. Majority of the medicinal properties of plants are attributed by secondary metabolites. These metabolites render color, flavor, and aroma to plants which are utilized in food and drug industries [2]. Moreover, herbal plants are widely used in several cuisines as spices and condiments [3]. The chemo-diversity of secondary metabolites corresponds to different biological functions. According to World Health Organization (WHO), about 80% of population are interested on the utilization of traditional medicine which involves botanical isolates [4]. In recent times, research is ongoing particularly with respect to the gene or gene clusters associated with secondary metabolite biosynthesis [5] and organ specific accumulation of secondary metabolites with therapeutic values [6]. To facilitate the investigation of mint based bioactive compounds, the present endeavor provides a comprehensive

overview of secondary metabolites and nutraceutical effects of two commercially important mints such as *Mentha arvensis* L. and *Mentha* × *piperita* L.

Mints are herbaceous plants with a collection of more than 60 species belonging to Lamiaceae family originated from Mediterranean basin and spread throughout the world by both natural and artificial means [7]. Mints are used as flavoring agents in food, beverage, chewing gums, and candies [8]. It is considered as healthy leafy vegetable because of its vitamins and mineral nutrients [9]. Due to the presence of potential secondary metabolites, mint was employed to treat various disorders since antiquity in ayurvedic and Chinese medicines [10]. The decoctions of mint aids in reduction of swelling, pain reliver, and is often used for the treatment of headache and eye redness, arthralgia, rubella, measles, chest, and hypochasm distension [10,11]. Numerous studies have evidenced that mint extracts can improve the digestive system, central nervous system, and respiratory system of the human body, and have anti-inflammatory antibacterial, antiviral, anticancer, antioxidation and other effects [12–14]. The abovementioned curing effects of mints are because of the occurrence of pharmaceutically valuable bioactive compounds. The main volatile components of mint include: menthol, menthone, menthyl acetate, menthofuran, and 1,8-cineol., etc. [15–18]. Non-volatile components present in mint are: flavonoids, phenolic acids, amino acids, nucleosides, terpenoids, etc., which are also the main active components of mint to play anti-inflammatory and antiviral effects [19,20]. The proportion and content of these components were affected by various factors such as growing environment, harvesting time, and variations in the species [21]. Among mint species, *M. arvensis* L. and *M.* × *piperita* L. are widely cultivated for the essential oil. *M. arvensis* is originated in the temperate climate of Europe, West Asia, and Central Asia [22]. *M.* × *piperita* is a natural hybrid between *M. viridis* and *M. aquatica* originated in the Mediterranean region [23]. The morphological differences of the two mint species are summarized in Table 1. Both mint species also displayed differences in content of essential oils. The essential oil of *M. arvensis* is made up of 30 to 50% menthol, 15 to 30% menthone, 3 to 10% menthyl acetate, and 1 to 5% other terpenes [24], whereas in *M.* × *piperita*, menthol accounted for about 36%, menthone 21%, menthyl acetate 7%, eucalyptol 7%, isomenthone 5%, neomenthol 4%, menthofuran 3%, D-limonene 2%, b-caryophyllene 2%, pulegone 1%, and b-pinene 1% [25]. Both mint species contributed to human health as excellent medicinal plants and raw materials for essential oil extraction.

Table 1. The morphological differences of *M. arvensis* and *M.* × *piperita*.

Species	***M. arvensis***	***M.* × *piperita***
Plant height	10–60 cm	30–100 cm
Stem	Purple at seedling stage and green at maturity, pilose	Purplish-red and glabrous
Leaf	Pale green, densely pilose along veins and sparsely puberulent elsewhere	Dark green, glabrous or below veins bristly and densely glandular
Flower	Corolla mauve, whorled on stems at leaf bases	Corolla white, lobes with pink halo, verticillaster form spica at the tips of stems and branches

The extracts of *M. arvensis* has been indulged in folklore medicine for the treatment of several diseases such as peptic ulcer, indigestion, skin allergies, respiratory diseases, etc. [26]. Various tissues of *M. arvensis* possess diverse medicinal properties. For instance, the decoctions obtained from leaf acts as diuretic agent, used to treat cold, asthma, rheumatism, jaundice, and other liver diseases [26]. *M. arvensis* oil, act as a natural source of anti-aflatoxigenic and antioxidant properties, protects the stored food commodities [27]. Furthermore, the essential oil provides a variety of health benefits, including antioxidant [28], anti-inflammatory [29], and antibacterial properties [30]. The essential oil from *M. arvensis* can serve as a natural pesticide [22]. Similarly, *M.* × *piperita* L. (peppermint) is a vital species in mint family with recognized pharmacological properties. It has been widely cultivated for its numerous benefits in agriculture, food, and medicinal purposes [31]. The

essential oil of *M.* × *piperita* consists of myriads of bioactive phytochemicals with potential to treat several ailments [32–34]. The essential oils and secondary metabolites extracted from both mint species consisted of various health benefits.

2. Phytochemicals of *M. arvensis* and *M.* × *piperita*

Diverse bioactive phytochemicals were present in leaves, stem, and root tissues of *M. arvensis* [35]. The major components in *M. arvensis* are alkaloids, flavonoids, polyphenols, tannins, cardiac glycosides, and eugenol [35]. Flavonoids and terpenoids are mostly present in the leaves whereas diterpenes occur in both leaves and stems [35]. The *M. arvensis* consists of monoterpenes such as menthone, isomenthone, menthofuran, menthyl acetate cineole, limonene, and sesquiterpenes such as viridiflorol [22,24]. Flavonoids such as luteolin, menthoside, isorhoifolin, rutin hesperidin were also identified in *M. arvensis* [36]. Further, it also contains phenolic acids like caffeic acid, chlorogenic acid, and rosmarinic acid [37,38]. Triterpenes like squalene, α-amyrin, urosolic acid and sitosterol and phytol compounds like tocopherols, carotenoids, choline, betaine, cyclenes, rosmarinic acid, and tannin were also identified in *M. arvensis* [28]. Interestingly, a unique component linarin (acacetin-7-O-β-D-rutionside) was detected in the flower tissue of *M. arvensis* [39]. Similarly, *M.* × *piperita* also consists of numerous phenolic compounds such as caffeic acid, rosmarinic acid, eriocitrin, luteolin-7-O-glucoside, gallic acid, p-Coumaric acid, chloregenic acid, sinapic acid, ellagic acid, hesperidin, and trans-ferulic acid [40–42]. Occurrence of flavones such as eriodictyol, naringenin, and hesperidin were identified in the leaf tissue of *M.* × *piperita* [43]. Leaf also consists of aglycones, palmitic acid, linoleic acid, linolenic acid, ascorbic acid, and soluble sugars [31]. Moreover, the presence of vital mineral nutrients such as potassium, calcium, sodium, phosphorus, zinc, and magnesium were also identified in the dried leaves of *M.* × *piperita* [44]. In general, the vital essential oil contents are present in the glandular trichomes of *M.* × *piperita* [11,45]. Phytochemical analysis of *M.* × *piperita* essential oil revealed the presence of several components such as menthone, iso-menthone, menthol, d-carvone, limonene, pulegone, and methyl petroselinate [46]. In addition, lignans and stilbenes were also identified in the extracts of *M.* × *piperita* [11]. Taken together, the occurrence of bioactive phytochemicals with diverse beneficial properties makes both mint species an economically important choice for cultivation.

3. Uses of *M. arvensis* and *M.* × *piperita*

Both *Mentha* species are widely utilized in food and beverage industries, cosmetics, agrochemicals, and herbal medicines due to presence of diverse phytochemicals [22,47,48]. The *Mentha* oil extracted from both species consists of a cooling effect, slight bitter taste, and strong aroma; due to these reasons, it can enhance the flavor and aroma of several products [48]. For instance, mint oil is used as the flavoring agent in candies, chewing gums, sauces, and beverages [47–50]. Moreover, the menthol-based cooling effect can act as a pain reliever which is a vital component in several pain-relieving balms and ointments [48–50]. Mentha-based dental products such as toothpastes and mouthwash causes a soothing cool effect in the oral cavities [49]. Further, *Mentha* oils are widely used essential oils for aromatherapy to relive stress and fatigue [51]. A recent study by Lin et al. [52] has demonstrated the changes occurring in electronencephalographic activity upon inhalation of peppermint oil under different visual stimuli. The results suggested that inhalation of peppermint oil enhanced the production of alpha waves in the pre-frontal area responsible for learning and thinking in white-sniffing group [52]. Additionally, the insect repellent property of mint oil is utilized to produce safer agro-chemicals and biopesticides [22]. The mint-based fodders are also employed in animal husbandry [53]. According to Masouri et al., [54] the supplementation of diet with peppermint oil increased the digestion of minerals and improved the meat quality in Japanese quails. Similarly, dietary supplementation of mint enhanced the egg laying capacity of hens [55]. Another wider usage of mint is in herbal medicines. Since antiquity mint is used to treat several ailments in various part of the world [46–50]. Mint are widely used to treat inflammation, bronchitis, toothaches, cramps,

fever, headaches, and sore throat, etc. [46–49]. Moreover, the extracts of mint are employed in the treatment against intestinal colic, digestive disorders, ailments associated with gall bladders, gastric ulcers, and other gastrointestinal diseases [46–50]. The immense positive benefits of mints are widely attributed by its phytochemical constitutes with nutraceutical effects. However, some reports also illustrated the side effects of *M.* × *piperita* essential oil such as headache, vomiting, nausea, gastrointestinal discomforts, and heartburn [46–49]. This denotes a deeper knowledge on the mode of action of phytochemicals on disease targets is required. Therefore, in the future, research will focus on the development of novel mint based herbal formulation and identification of novel drug molecule with higher efficacy and lesser side effects has to be conducted.

4. Antioxidant Properties of *M. arvensis* and *M.* × *piperita*

Detoxification of harmful reactive oxygen species in higher concentrations generated in biological systems is inevitable for the proper physiological and metabolic functioning of an organism. The oxidative stress caused by these free radicals damages cellular proteins, lipids, and DNA molecules which results in diverse pathological conditions/diseases [56]. Natural compounds with antioxidant properties particularly from plant origin are always in demand. Plants consists of various phytochemicals with antioxidant compounds which facilitate the recovery from oxidative damages. These antioxidant property of plant extracts can be validated using various in vitro assays such as 2,2-diphenyl-1-picrylhydrazyl) (DPPH) radical scavenging, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) ($ABTS^+$) analysis, and reducing power assays [47,57,58]. In most of these assays, the free radicals are propagated in a media which can be detoxified by the extract if it has antioxidant capacity, and this can be spectrophotometrically measured and compared with control like ascorbic acid. In general, polyphenolic compounds readily take part in the transfer of electrons and hydrogen atoms which attributes their antioxidant properties. To assess these potentials, the ability of the plant extract to reduce iron in the reaction mixture by the extracts are tested using various in vitro assays.

Apart from this mechanism, the phytochemicals can also act as chain terminators of free radicals making the unstable radicals into non-reactive stable compounds [43]. Several studies have evidenced the antioxidant properties of *M. arvensis* and *M.* × *piperita* using the invitro antioxidant assays. For instance, Dorman et al. [43] illustrated the antioxidant potentials of *M.* × *piperita* extracted using different solvents which resulted in extraction efficiencies with different quantities and qualities. Among the solvents employed, methanolic extracts of *M.* × *piperita* leaves displayed higher quantitative levels of total phenols and flavonoids. However, the significant qualitative antioxidants were observed in the ethanolic extracts of *M.* × *piperita* with eriocitrin, rosmarinic acid, and naringenin-7-o-glucoside. Extracts of *M.* × *piperita* displayed significant antioxidant property evidenced from increased reduction of iron(III), higher efficiency in DPPH, $ABTS^+$, and H_2O_2 free radical scavenging properties [43]. Recent report by Hammad Al-Mijalli et al. [59] determined the volatile chemical compounds in *M.* × *piperita* and evidenced its antioxidant properties. Likewise, the *M. arvensis* extracts illustrated significant free radical scavenging activities. Biswas et al. [28] validated antioxidant potentials of *M. arvensis* qualitatively using thin layer chromatography (TLC) and quantitatively by using DPPH assay. Moreover, the aqueous extracts of *M. arvensis* displayed varying levels of antioxidant properties in different assays such as DPPH, $ABTS^+$, and phospholipid peroxidation assay [28]. Antioxidant properties of *M. arvensis* and *M.* × *piperita* were exerted by various phytochemicals present in different tissues are listed in Table 2. Numerous research studies support the presence of free radical scavenging properties of *M. arvensis* and *M.* × *piperita*, however, in order to proceed forward, studies unveiling the metabolite specific antioxidant mechanisms needs to be established. Further, molecular analysis of metabolic pathways responsible for the synthesis of potential antioxidants in both species will aid in the metabolic engineering of vital phytochemicals with antioxidant potentials. Moreover, a proper characterization

of antioxidant compounds and precise extraction approaches needs to be devised for the holistic utilization of the *Mentha* for large-scale production of antioxidant compounds.

Table 2. The phytochemicals with antioxidant potentials present in *M. arvensis* and *M.* × *piperita*.

Species	Tissue/Sample Extract	Class	Compound	References
M. arvensis	Essential oil	Terpenoid	Geranyl acetate	[60]
			Pulegone/lsopulegone	[60]
			Menthonel lsomenthone	[60]
			Menthone	[60]
			Menthyl acetate	[61]
			Menthone	[61]
			Terpenoid	[62]
			Menthol	[61,63]
			Menthyl acetate	[63]
			Pulegone	[63]
			Limonene	[63]
			Isomenthone	[63]
			Menthone	[63]
			Isomenthone	[63]
			Menthol	[61,63]
M. × *piperita*	Rhizome	Phenolic acids	Protocatechuic aldehyde	[64]
			Luteolin-7-O-rutinoside	
			Caffeic acid	
			Salvianolic acid	
			Lithospermic acid	
			Salvianolic acid B	
			Hesperetin-7-O-rutinoside	
			Rosmarinic acid	
			Eriodictyol-7-O-rutinoside	
M. × *piperita*	Essential oil	Terpenoid	Sabinene	[32]
			β-Pinene	
			β-Myrcene	
			α-Terpinene	
			Limonene	
			1,8-Cineole	
			cis-Sabinene hydrate	
			Linalool	
			Menthone	
			Menthofuran	
			δ-Terpineol	
			neo-Menthol	
			Menthol	
			Terpinen-4-ol	
			Pulegone	
			Piperitone	
			Geranyl acetate	
			(E)-β-Farnesene	
			Germacrene D	
			Elixene	
			Viridiflorol	
			Monoterpene	
			Hydrocarbons	
			Oxygenated monoterpenes	
			Sesquiterpene hydrocarbons	

Table 2. *Cont.*

Species	Tissue/Sample Extract	Class	Compound	References
M. × *piperita*	Leaf	Phenols	Sinapic acid Gallic acid Catechin Caffeic acid Chloregenic acid Rutin Quercetin p-Coumaric acid Coumarin Carvacerol Vanilin Trans-ferulic acid Hesperedin Ellagic acid Eugenol Hesperetin	[65]
M. × *piperita*	Leaf	Flavanones	Naringenin Eriodictyiol Hesperetin Apigenin Luteolin Diosmetin	[60]

5. Anti-Inflammatory Activities of *M. arvensis* and *M.* × *piperita*

In general, inflammation is a defense response to injury or infection to remove exogenous substances and facilitate self-healing. Inflammatory responses are triggered by a cascade of molecular mechanism and one of the main regulations is mediated by mitogen activated protein kinases (MAPKs)/nuclear factor-kappa B (NF-kB) signaling [66]. For this response, NF-kB is activated by mitogen activated protein kinases (MAPKs). Consequently, NF-kB can significantly influence the production of vital pro-inflammatory factors such as tumor necrosis factor-α (TNF-α), interleukin (IL-6), and IL-1β [29]. Similarly, inflammatory reactions such as pain, fever, edema, and dysfunction can be mediated by nitric oxide (NO) and prostaglandin E_2 (PGE_2) signaling mediator regulated by inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) [67,68]. Essential oils (EOs) of *M. arvensis* and *M.* × *piperita* have been evaluated for their anti-inflammatory activities in both in vivo or in vitro conditions. Recently, Kim et al. [29] reported the anti-inflammatory effects of *M. arvensis* essential oil in atopic dermatitis which is a chronic inflammatory skin disease. The molecular analysis revealed the essential oils of *M. arvensis* attenuated the inflammatory mediators in lipopolysaccharide (LPS)-stimulated RAW 264.7 macrophages. Further, the essential oils also inhibited phosphorylation of P65 and ERK necessary for activation of inflammatory response in NF-kB signaling pathway [29].

Similarly, in animal models, the immune-modulating effects of *M.* × *piperita* were evaluated. According to Atta et al. [68], pre-injection of the ethanol extract (200 and 400 mg/kg) of *M.* × *piperita* into mice significantly inhibited 49–50% acute inflammation of ear edema induced by topical xylene treatment. In another study, Mogosan et al. [69] identified that essential oils of *M.* × *piperita* attenuated the rat paw edema induced by λ-carrageenan. The in vitro anti-inflammatory effect was evaluated by measuring the secretion of proinflammatory cytokines including interleukin (IL)-1β, TNF-α, IL-6, etc., or inflammatory mediators like NO and PGE_2 [69]. The EOs of *M.* × *piperita* and *M. arvensis* displayed similar mode of action to induce anti-inflammatory response by affecting the NF-κB signaling pathway. For instance, Sun et al. [68] reported that *M.* × *piperita* essential oils effectively ceased NO and PGE_2 production in LPS-stimulated RAW 264.7 macrophages. A similar anti-inflammatory effect of essential oil of *M.* × *piperita* was also found in other LPS-stimulated cells, such

as porcine alveolar macrophages (PAMs) [70] and HaCaT cells [29]. Menthol is the fundamental constitute of EOs derived from *M.* × *piperita* and *M. arvensis*, which significantly suppresses the production of TNF-α, IL-1β, LTB4, and thromboxane B2 in LPS-stimulated human monocytes [71,72]. According to Juergens et al. [71], 1,8-cineole extracted from peppermint also possesses the ability to suppress the inflammatory mediating compounds [71]. Based on the above research, it can be conceived that essential oils of *M. arvensis* and *M.* × *piperita* exert repressing effects on cytokines or inflammatory mediators involved in the ERK/NF-κB signaling pathway to provide an anti-inflammatory response (Figure 1). Thus, the essential oils of these mint species can be utilized for the herbal formulations associated with anti-inflammatory medicines.

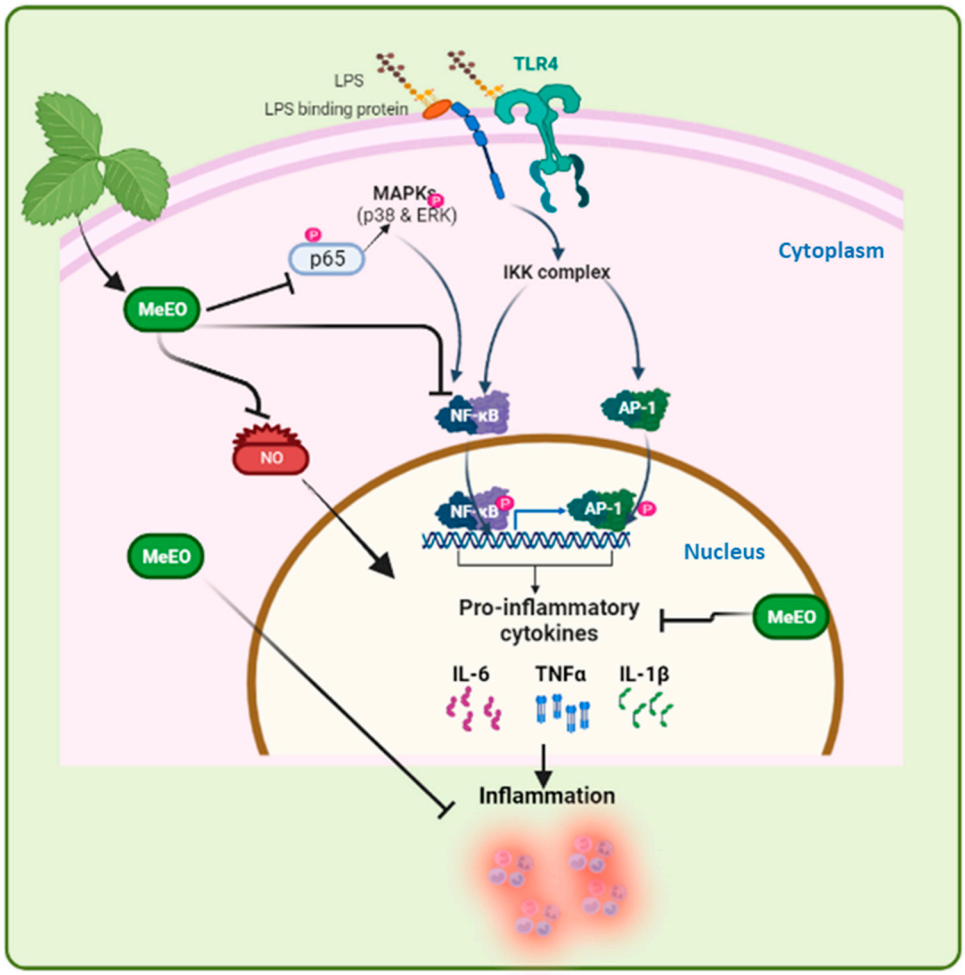

Figure 1. Schematic representation illustrating the anti-inflammatory activity exerted by *M. arvensis* and *M.* × *piperita* essential oils. MeEO, *Mentha* essential oil; LPS, Lipopolysaccharides; TLR4, Toll like receptor 4; MAPK, mitogen activated protein kinases; NF-kB, nuclear factor-kappa B; IKK, IκB kinase; AP1, Activator Protein 1, NO, nitric oxide; TNF-α, tumor necrosis factor-α; The above figure is drawn using BioRender illustrations.

6. Anti-Bacterial Activity of *M. arvensis* and *M.* × *piperita*

The antibacterial activities of *M.* × *piperita* and *M. arvensis* have been investigated extensively. The extracts can potentially inhibit the growth of various Gram-positive and Gram-negative bacteria (Table 3). Several reports illustrated the antibacterial activities of these extracts against pathogenic bacteria such as *Staphylococcus aureus* [30], *S. epidermidis* [73], *Salmonella typhimurium* [74], *Klebsiella pneumoniae* [75], etc. Moreover, studies have also compared the anti-bacterial activity of *M.* × *piperita* and *M. arvensis*, but the results were inconsistent. For instance, Hussain et al. [30] identified that the essential

oil of *M. arvensis* possess better anti-bacterial properties than *M.* × *piperita*. For example, the *M. arvensis* displayed a minimum inhibitory concentration (MIC) of 20.3 ± 1.0 µg/mL for *Bacillus subtilis*, whereas the MIC of 123.4 ± 5.8 µg/mL was observed upon *M. piperita* treatment [30]. However, to the same strain, Heydari et al. [76] reported a MIC of 10 mg/mL with *M. arvensis* treatment while the MIC of *M.* × *piperita* was reported as 0.1 mg/mL. This disparity in the results can be due to the differences in the chemical components of the extracts, plant materials from different geographical environment, seasonality, maturity of the plant, and the method of oil isolation [75–78]. In the studies above, higher percent of menthol were found in the essential oils with better antibacterial activities. Menthol, a cyclic monoterpene alcohol, has been confirmed with good antimicrobial activity [79–81]. It was identified as the major antimicrobial compound in *M.* × *piperita* and *M. arvensis* oils [30,82]. The anti-bacterial mechanism of menthol has not been clearly elucidated, however it can be hypothesized as membrane-related inhibitory mechanisms [81]. Likewise, studies on the anti-bacterial function of terpenoids also suggested that their site of action was at the phospholipid bilayer, which would modify the membrane permeability and cause leakage of intracellular substances [83].

Further, Shalayel et al. [73] evaluated the anti-bacterial effect of *M.* × *piperita* extracted using different reagents, and discovered that the ethyl acetate extract had strongest anti-bacterial effects on the tested pathogens, followed by the chloroform, ethanol, and methanol extracts. On the other hand, Singh et al. [75] reported that ethyl acetate extract of *M.* × *piperita* possessed more inhibitory activity, indicating the primary importance of solvent used for extraction in determining the chemical composition. Additionally, Singh et al. [75] identified that the *M.* × *piperita* oil is more effective against Gram-positive than Gram-negative bacteria. Similarly, Gochev et al. [84] evaluated the antimicrobial activity of Bulgarian peppermint oil and illustrated that peppermint oils are more effective against Gram-positive bacteria than Gram-negative bacteria. This might be due to the existence of lipopolysaccharides in the outer membrane of Gram-negative bacteria, which could enhance their resistance to antibacterial substances [82]. In addition, *M. arvensis* leaves displayed strong anti-bacterial effects against multidrug resistant *Acinetobacter baumannii* [85]. The essential oil isolated from the fresh leaves of *M. arvensis* ceased the growth of five bacterial strains such as *S. aureus, B. subtilis, S. pyogenes, E. coli, and P. aeruginosa*, respectively [86,87]. The anti-bacterial activity of *M.* × *piperita* and *M. arvensis* is due to the occurrence of mixture of phytochemicals particularly the essential oil components. In addition, based on the observed results, it can be assumed that the synergistic action of diverse phytochemicals in varying quantities present in the extracts could lead to the difference in the bactericidal activity of the extracts. However, the similar combinatorial activity of the phytochemical can also lead to lower effects against different bacterial strains. Therefore, future studies should be designed to delineate the primary constituent responsible for the anti-bacterial activity along with the molecular mechanism of action. Further, research on pathogen specific interaction anti-bacterial components in mints will facilitate its industrial and medicinal application.

Table 3. Anti-bacterial activity of *M.* × *piperita* and *M. arvensis*.

Species	Sample Extract or Essential Oil	Origin of Bacterial Culture	Bacteria	[z] MIC (mg/mL)	References
M. × *piperita*	Leaf extract	Pure cultures	*Staphylococcus aureus ATCC 25923*	12.0	[30]
			Bacillus subtilis ATCC 10707	12.3	
			Escherichia coli ATCC 25922	31.04	
M. arvensis	Leaf extract	Pure cultures	*Staphylococcus aureus ATCC 25923*	3.0.5	[30]
			Bacillus subtilis ATCC 10707	2.03	
			Escherichia coli ATCC 25922	33.03	

Table 3. *Cont.*

Species	Sample Extract or Essential Oil	Origin of Bacterial Culture	Bacteria	[z] MIC (mg/mL)	References
M. × *piperita*	Essential oil	Pure cultures	*Staphylococcus aureus ATCC 9144*	8.3	[88]
			Enterococcus faecalis CIP 103907	8.3	
			Listeria monocytogenes CRBIP 13.134	10	
			Enterobacter aerogenes CIP 104725	>80	
			Escherichia coli CIP 105182	40	
			Pseudomonas aeruginosa CRBIP 19.249	>80	
			Salmonella enterica CIP 105150	8.3	
			Salmonella typhimurium ATCC 13311	13.3	
			Shigella dysenteria CIP 54.51	5.8	
M. × *piperita*	Essential oil	Pure cultures	*Escherichia coli αDH5*	1.13	[89]
			Escherichia coli ATCC 25922	1.13	
			Pseudomonas aeruginosa	2.25	
			Pseudomonas fluorescens	2.25	
			Bacillus subtilis	1.13	
			Staphylococcus aureus	1.13	
M. × *piperita*	Essential oil	Clinical oral isolates	*Staphylococcus aureus*	62.67	[90]
			Streptococcus pyogenes IBR S004	63.00	
			Streptococcus mutans IBR S001	60.33	
			Lactobacillus acidophilus IBR L001	27.00	
			Streptococcus salivarius IBR S006	34.66	
			Streptococcus sanguinis IBR S002	28.66	
			Enterococcus faecalis IBR E001	23.86	
M. × *piperita*	Extract of aerial part	Clinical isolates from nosocomial patients	*Staphylococcus aureus*	5.00	[73]
			Staphylococcus epidermidis	2.50	
			Streptococcus pyogenes	1.25	
			Enterococcus faecalis	2.50	
			Escherichia coli	5.00	
			Klebsiella pneumoniae	10.00	
			Pseudomonas aeruginosa	20.00	
			Seratia marcescens	10.00	
			Acinetobacter baumannii	40.00	
			Stenotrophomonas maltophilia	40.00	
M. × *piperita*	Essential oil	Pure cultures	*Staphylococcus epidermidis*	2.00	[76]
			Staphylococcus aureus	10.00	
			Bacillus subtilis	0.10	
			Bacillus cereus	0.08	
M. arvensis	Essential oil	Pure cultures	*Staphylococcus epidermidis*	10.00	[76]
			Staphylococcus aureus	10.00	
			Bacillus subtilis	10.00	
			Bacillus cereus	10.00	
M. × *piperita*	Essential oil	Pure cultures	*Listeria monocytogenes PTCC 1163*	12.50	[74]
			Salmonella typhimurium ATCC 13311	25.00	
M. arvensis	Essential oil	Clinical isolates from vaginal swabs	*Streptococcus agalactiae ATCC 13813*	1.80	[91]
			Lactobacillus spp.	1.80	

[z] MIC = Minimum inhibitory concentration.

7. Antifungal Activity of *M. arvensis* and *M.* × *piperita*

The antifungal activities of *M. arvensis* and *M.* × *piperita* have been evidenced in various reports and most of the effects are due to the occurrence of essential oils. *Candida species* are opportunistic fungal pathogens to humans. Candidiasis caused by the infection of *Candida species* has a wide spectrum, varying from mild infection of skin or mucous membrane to severe invasion of organs [92]. Studies on the anti-fungal activities showed that the essential oils of *M.* × *piperita* and *M. arvensis* could inhibit the growth of *Candida species* and prevent the formation of biofilm [93–96]. The antifungal activity of *M.* × *piperita*

essential oil was comparable to that of amphotericin-B [93]. The formation of biofilm is the survival mode of *Candida species*, which can also contribute to its pathogenesis, and drug resistance. According to Saharkhiz et al. [95], the essential oil of *M.* × *piperita* inhibited the biofilm formation of *Candida albicans* and *C. dubliniensis* at concentrations up to 2 µL/mL. The antifungal mechanism of *M.* × *piperita* essential oil involves downregulation of the expression of some potential genes, such as secreted aspartyl proteinases (SAP 1, 2, 3, 9, 10) and hyphal wall protein 1 (HWP1) [93]. The essential oil of *M.* × *piperita* is also reported to be effective in inhibiting the growth of dermatophytes. The essential oils of *M.* × *piperita* significantly ceased the growth of pathogenic fungi belonging to dermatophytes such as *Trichophyton mentagrophytes*, *Microsporum canis*, and *M. gypseum* [97–99]. The antimycotic effect of *M.* × *piperita* essential oil against *Malassezia pachydermatis*, a common cause of dermatitis in dogs were illustrated by Nardoni et al. [100]. Similarly, the antifungal activities of *M.* × *piperita* against various plant pathogens have been widely studied. For instance, Rachitha et al. [101] discovered that *M.* × *piperita* essential oils showed inhibitory activity against *Fusarium sporotrichioides*, a filamentous fungi that contaminate corn and corn-based products. The application of *M.* × *piperita* essential oil against the postharvest fungi *Botrytis cinerea*, *Monilinia fructicola*, *Penicillium expansum*, and *Aspergillus niger* identified to be effective against all tested fungi [102]. The inhibitory effect of *M.* × *piperita* essential oil against fungal pathogens of vegetables and mushrooms, including *Botrytis cinerea*, *Sclerotinia sclerotiorum*, *Fusarium oxysporum*, *Phytophthora parasitica*, *Pythium aphanidermatum*, *Alternaria brassicae*, *Cladobotryum mycophilum*, and *Trichoderma aggressivum f.sp. europaeum* were reported by Diánez et al. [103].

The antifungal property of *M. arvensis* essential oils enabled them to be applied in the field of food preservation. The augmentation of *M. arvensis* essential oil into gelatin edible coatings generated transparent film to prevent the infection of *Botrytis cinerea* and *Rhizopus stolonifera* in food and vegetable [104]. The ethanolic extracts of *M. arvensis* were assayed for antifungal activity against the strains of *C. albicans*, *C. tropicalis*, and *C. krusei*, and a potentiation effect was observed by Santos et al. [96]. The fungicidal activity for menthe, a volatile oil and principal constituent, has been established against *Rhizoctonia solani* and *Fusarium moniliforme*. It was also evaluated for antimycotic efficacy against *F. oxysporum* and *T. mentagrophytes* [105]. Till date, the mechanism of antifungal action by the essential oils are not revealed however earlier researches suggested that the mechanism can be due to the distortion of plasma membrane permeability of the fungus [106]. This result in the alteration of ion transport, respiration, and other vital metabolism of fungi. Overall, the above reports suggested efficient antifungal activity of *M. arvensis* and *M.* × *piperita* essential oils primarily mediated by alteration of plasma membrane permeability of the fungi as one of the modes of action. However, the occurrence of single or multiple metabolites with antifungal activity in *Mentha* require to be investigated. Further, existence of other possible mode of actions exerted by the bioactive phytochemicals in *Mentha* against pathogenic fungi needs to be elucidated.

8. Anticancer Activities of *M. arvensis* and *M.* × *piperita*

Cancer is an increasingly serious health problem worldwide and has replaced heart disease as the leading cause of death worldwide [107]. Although the field of oncology medicine has made great progress in the present era, there are still several issues that need to be solved to improve cancer treatment. In the past decade, much research has focused on finding new therapies to reduce side effects caused by modern medicine [108]. Novel drug molecules with high efficiency, efficacy, less side effects and low environmental impact are desirable for the cancer treatment. To date, the search for the effective drug against most cancers are still in progress. Plant-based bioactive compounds provide opportunities for innovation in drug discovery. Several phytochemicals play an important role in the prevention and treatment of cancer. Among many phytochemicals with diverse structures, essential oils have attracted much attention due to their rich biological activities [109]. *M. arvensis* and *M.*× *piperita* also play important roles in the field of anticancer drug devel-

opment as major *Mentha* oil raw materials. Nano-emulsion of *M. arvensis* essential oil demonstrated high induction effect on early and middle apoptosis in anaplastic/aggressive thyroid cancer cells [110]. Likewise, methanol extract and essential oil from six different *M.* × *piperita* plants were effective against Vero, Hela, and Hep2 cancer cell lines [83]. In detail, the methanol extract has higher cytotoxic activities than essential oil for Vero and Hela whereas, the effect was reversed in Hep2 cancer cell line. These results indicated that there are differences in the effective components or mode of action in the extracts for cytotoxic activity on different types of cancer cells [111]. According to Jain et al. [112], the *M.* × *piperita* extracts isolated with different organic solvents or water had different cytotoxic activity against six common human cancer cells. The results suggested that chloroform and ethyl acetate extracts induced significant dose-dependent and time-dependent anticancer activity, leading to G1 cell cycle arrest and mitochondria-mediated apoptosis, perturbation of oxidative balance, up-regulation of Bax genes, increased expression of p53 and P21, and induction of pro-inflammatory cytokine responses [112]. In most cases tumor formation is frequently accompanied by the development of new blood vessels. The extract of *M. arvensis* could facilitate the prevention of cancer by inhibiting the generation of blood vessels which was evidenced through chick chorioallantoic membrane assay [113]. In another study, *M.* × *piperita* extract not only restrained skin papilloma by influencing the activation/detoxification of the carcinogen but also improved cellular resistance to radiation through enhancing the antioxidant mechanism [114]. Likewise, *M. arvensis* extract suppressed the growth and induced apoptosis against HepG2 cell lines which was observed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay [47]. Moreover, the *M. arvensis* also displayed anti-cancer activity against eight human cancer cells from six different origins such as breast, colon, prostate, lung, leukemia, and glioblastoma [47]. Further, green silver nanoparticles synthesized from *M. arvensis* displayed a promising role against the breast cancer cell line with less toxic to normal cells, non-mutagenic, mediated caspase 9-dependent apoptosis in MCF7 and MDA-MB-231 cells [115]. An essential oil which contains menthol, menthone has anticancer property in treating anaplastic thyroid cancer cells by nanoemulsion method [110]. According to Weecharangsan et al. [116], essential oils of *M. arvensis* showed cytotoxic activity with IC_{50} value of 142.0 ± 92.2 and 243.3 ± 151.1 µg/mL against KB cells and with IC_{50} value of 178.4 ± 92.1 and 779.4 ± 673.3 µg/mL against HeLa cells. Moreover, the *M. arvensis* extract contains Rosmarinic acid(Ra), a natural phenolic compound which induced dose-dependent cell death in cultured HepG2 cells and mRNA expression analysis confirmed the down regulation of anti-apoptotic gene Bcl2 with upregulation of proapoptotic genes like Bax and ERK2 [117]. Similar to other aromatic herb extracts, monoterpenes, sesquiterpenes, oxygenated monoterpenes, oxygenated sesquiterpenes, and phenolics, among others, play key roles in the anticancer mechanism of mint extract. The main mechanism of chemoprophylaxis of these compounds is protection against oxidation, mutation and proliferation, enhancement of immune function and monitoring, enzyme induction and improvement of detoxification ability, regulation of multidrug resistance, and synergistic action. However, more research on the identification of specific components and their mechanism of action needs to be performed to promote the treatment of cancer by natural products such as mint extracts in the future.

9. Extracts of *M. arvensis* and *M.* × *piperita* in Radiation Therapy

Radiotherapy is a vital method for the treatment of malignant tumors. About 50% of cancer patients need radiation therapy in the course of cancer treatment, and about 40% of cancers can be suppressed with radiation [118]. At present, targeted radiations towards cancerous cells without affecting the normal cells is an immensely researched area to provide effective anti-cancer treatment [119]. In the chemical radiation therapy, sensitizers or protectors possess the ability to guard the normal cells to an extent from the damages caused by radiations [120]. However, the radiation protectors discovered earlier, such as 2-(3-aminopropylamino) ethylsulphanyl phosphonic acid (WR-2721), are toxic to

cells at the optimal protective concentration [121]. Therefore, research has been focused on the identification of effective plant/natural-product-based radiation protectors for cancer treatments. One of the promising alternates is the extract of *M. arvensis.* According to Jagetia and Baliga [122], mice fed with different doses of *M. arvensis* extract had significantly decreased the side effects of gamma radiations in comparison with the control. The results showed that the optimal protection was provided by feeding 10 mg/kg *M. arvensis* extract, which was much lower than the toxic dose (1000 mg/kg). Similarly, radiation protection function was also identified in *M.* × *piperita* [123–125]. Under in vivo conditions in the mice model, *M.* × *piperita* extract significantly improved serum alkaline phosphatase and declined serum acid phosphatase activities. Alkaline and acid phosphatase plays an important role in the maintenance of cell permeability [126–128]. These reports demonstrated that *M.* × *piperita* alleviates the damages to animal cell membranes caused by radiation to some extent. Likewise, *M.* × *piperita* extract aided in the recovery of intestinal mucosa [124], bone marrow [125], and testicles [129] from radiation damages in mice. This illustrates that *Mentha* extract consists of promising phytochemicals which can prevent the cellular damages caused by radiations. It is apparent from the above studies that the extracts of *M. arvensis* and *M.* × *piperita* can act as vital components for recovery from damages caused by radiations but the exact rationale behind the anti-radiation property needs to be identified.

10. Conclusions and Future Perspectives

Versatile nutraceutical potentials of *M. arvensis* and *M.* × *piperita* have been evidenced from various studies denoting their enormous pharmaceutical importance, most of which has been attributed to its antioxidant, anti-microbial, anti-cancerous, and anti-inflammatory properties. The administration of *M. arvensis* and *M.* × *piperita* under various pathological conditions facilitate the recovery of diseases and aids in the prevention of detrimental ailments. Particularly, the occurrence of volatile essential oils in leaves, stems, and roots consists of the disease combating potentials which can be utilized for discovery of novel drugs with higher efficacy and lesser side effects. Even though mint consists of numerous economic and health benefits, to date, there is a scarcity of knowledge in the aspects of quality and quantity of the phytochemicals and choice of genotypes to be used as raw materials for large-scale industrial usage. In addition, the presence of excessive flavor or aroma in mint can negatively influence the organoleptic traits and reduce the consumer quality of the products. Therefore, research needs to address the abovementioned shortcomings to enhance the elite varieties of mint with optimal phytochemicals. Further, clinical trials with *Mentha* for diverse disorders should be initiated to validate the potential of the natural herbal medicines in human. Additionally, appropriate channel of knowledge on the method of consumption, elucidation of molecular mechanism behind the antioxidant, anti-cancer, and anti-microbicidal effects of *M. arvensis* and *M.* × *piperita* needs to be devised. In addition, application of current omics based approaches to unveil the metabolic pathways and candidate genes involved in the essential oil biosynthesis will facilitate the utilization of these *Mentha* species in large-scale in food and pharmaceutical fields.

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