IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON HERBAL DRUG USED IN SOME DISEASE AFTER ANTIMICROBIAL DRUG RESISTANCE

Muskan Gupta[1], Shubham Gupta[1], Reetu Chauhan[1], Anil kumar Jangid[1] , Nitin Kumar[1]

[1]Assitant Professor, [2]Assistant Professor, [3]Assistant Professor, [4]Assistant Professor, [5]Professor
[1]Department of Pharmaceutical Chemistry,
[1]Lords University, Alwar, Rajasthan, India

Abstract : The increasing incidence of drug- resistant pathogens raises an urgent need to identify and isolate new bioactive compounds from medicinal plants using standardized modern analytical procedures. Medicinal plant-derived compounds could provide novel straightforward approaches against pathogenic bacteria. This review explores the antimicrobial activity of plant-derived components, their possible mechanisms of action, as well as their chemical potential. Multidrug-resistant (MDR) bacteria have become more prevalent in recent times owing to the inappropriate and irrational use of antibiotics, which provides favorable conditions for the selection of antibiotic-resistant mutants. The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future is still uncertain. Research on the mechanisms of action, interplay with other substances, and the pharmacokinetic and/or pharmacodynamic profile of the medicinal plant extracts should be given high priority to characterize them as potential antimicrobial agents.

Keywords- Isolate, medicinal, pathogenic, antimicrobial, antibiotic

I. INTRODUCTION

Multidrug-resistant (MDR) bacteria have become more prevalent in recent times owing to the inappropriate and irrational use of antibiotics, which provides favorable conditions for the selection of antibiotic-resistant mutants [1]. Resistance against all classes of antibiotics has been described, which leads to a constant need for the development and production of new drugs. However, difficulties in the identification of new substances with both high effectiveness and low toxicity have resulted in only a few new antibiotic classes being discovered since the 1970s. [2]

Even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents. [3]

The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future is still uncertain. Therefore, actions must be taken to reduce this problem, for example, to control the use of antibiotic, develop research to better understand the genetic mechanisms of resistance, and to continue studies to develop new drugs, either synthetic or natural. The ultimate goal is to offer appropriate and efficient antimicrobial drugs to the patient. From 1980 to 1990, Montelli and Levy documented a high incidence of resistant microorganisms in clinical microbiology in Brazil. This fact has also been verified in other clinics around all over world. The problem of microbial resistance is growing and the outlook for the use of antimicrobial drugs in the future is still uncertain. Therefore, actions must be taken to reduce this problem, for example, to control the use of antibiotic, develop research to better understand the genetic mechanisms of resistance, and to continue studies to develop new drugs, either synthetic or natural. [4]

According to World Health Organization medicinal plants would be the best source to obtain a variety of drugs.[5] About 80% of individuals from developed countries use traditional medicine, which has compounds derived from medicinal plants. Therefore, such plants should be investigated to better understand their properties, safety and efficiency.[6]

Synthetic antimicrobials and antibiotics have been used for a long time against different infectious diseases both in human and animals. The main drawback in antimicrobial chemotherapy is the growing antimicrobial resistance which makes the treatments less effective [7]. Therefore, the recent studies had given emphasize on the use of alternative natural products, especially which are obtained from plants [8,9]

Infectious diseases are the leading cause of death worldwide; this has become a global concern. The wide use of antibiotics in the treatment of bacterial infections has led to the emergence and spread of resistant strains; even very low concentrations of antibiotics released into the environment can enrich the population of resistant strains [10]. There is an urgent and imperative need to develop novel therapeutics, new practices, and antimicrobial strategies for the treatment of infectious diseases caused by multidrug-resistant microorganisms. This has intensified the search for novel therapeutic leads against fungal, parasitic, bacterial, and viral infections. The discovery of new antibacterial compounds as suitable substitutes for conventional antibiotics might be a possible solution to this problem [11].

Plants and plant extracts have been used as traditional medications for many centuries. Volatile compounds of plant extracts, particularly essential oils (EOs) are known as a secondary plant metabolite which had been used primarily in aromatherapy, cosmetics and medicinal

purposes [12]. Various essential oils of different plants such as thyme, oregano, mint, cinnamon, cumin, salvia, clove, and eucalyptus have been observed to possess strong antimicrobial properties [13].

Various plants are discussed below-

1.1 Majoram

Biological name- *Origanum majorana*
Origanum majorana also called sweet marjoram, perennial plant of the mint family (Lamiaceae), grown as culinary herb. Its fresh or dried **leaves and flowering tops** are used to season many foods, imparting a warm, aromatic, slightly sharp, and bitterish flavour.
Botanical Description and Morphological Features-
It is a bushy half hardy perennial sub shrub that annually grows upto 30-60 cm height. The stems are straight, round and hairy in appearance and green in colour while leaves are greyish green in coloration. Marjoram have tiny white or pale pink flowers that bears oval and dark brown seeds. Marjoram (Origanum majorana L.) is a tender, perennial herb which belongs to family Labiatae and was formally classified as Majorana hortensis Moench [14]. It is generally called as "sweet marjoram" and found native to Eastern Mediterranean regions of the world.
Essential chemical constituent-
The essential oil extracted from various species of marjoram is of high nutritional value and extreme therapeutic potential owing to the presence of volatile aromatic compounds such as eugenol, citral, geranyl cetate, cadinene, ocimene, linalyl acetate, carvacrol, terpineol, linalool and various other terpenes. Due to anti-bacterial and anti-inflammatory effects, this oil has been used to treat rheumatism, muscular pains and flatulence. Some major chemical constituents of this plant include α-terpineol, terpinen-4-ol, p-cymene and myrcene [15]. The dried and fresh flowers and leaves of origanum are abundantly used as flavoring agent in various food industries. The alcoholic extracts and essential oil obtained from this plant via steam distillation mainly constitutes terpinen-4-ol along with the small amount of (+)-cis-sabinene hydrate [16] which is responsible for specific fragrance and characteristic flavor. In addition to that, α-terpinene, c-terpinene and terpinolene are also found as major components along with carvacrol and thymol [17-18-19]. The anti-oxidant potential of essential oil of majoram [20] and its relevant purified substances [21] has also been reported to found.
Drug resistance effect-
investigations demonstrated the antibacterial, efflux pump inhibitory, and antibiofilm-forming effect of sweet marjoram EO and its main monoterpenes against the tested bacteria.

The antibacterial activity of the EO was shown against sensitive and drug resistant S. aureus, and E. coli strains with MIC values of 0.125–0.250% (Table 1). These data are in accordance with previous studies which proved the inhibitory activity of sweet marjoram EO against S. aureus and S. pyogenes with MICs of 125 and 250 g/mL, respectively [22]. In these studies, higher concentrations and/or other bacterial strains were applied (MIC value 4 mg/mL against S. aureus clinical isolate, and S. aureus ATCC 29213) [23].

Among the tested six main monoterpenes of EO (terpinen-4-ol, sabinene, sabinene-hydrate, -terpinene, -terpinene, and linalool), mainly terpinen-4-ol, -terpinene, and linalool contribute to the antibacterial activity of EO, as demonstrated by their MIC values between 30–61 mM (Table 2). Our data are in agreement with earlier reports on the antimicrobial effect of these compounds [24,25]. Differences could not be observed between the pairs of sensitive and resistant strains. Among the EO constituents terpinen-4-ol can be highlighted because of its highest concentration in EO, and highest activities against E. coli ATCC 25922 and E. coli AG100 (30 mM).

With the aim of re-sensitizing antibiotic-resistant bacteria, efflux pump inhibition could be applied to overcome the resistant phenotype [26,27].

In our work, extracts of EO of O. majorana and its monoterpenes were assayed for efflux pump inhibitory activity in drug resistant and sensitive S. aureus and E. coli strains (Table 4). Among the EO constituents, only sabinene was an effective efflux pump inhibitor in the sensitive E. coli strain. In the case of S. aureus strains, EO and sabinene hydrate exhibited moderate potency on the drug-resistant phenotype. Therefore, Gram-negative, and Gram-positive bacteria have different susceptivity to efflux pump inhibitors, which can be explained by their different cell wall compositions [28].

In our experiments, the antibiofilm effects of the extracts, EO and its monoterpenes were tested in sub-MIC concentration (MIC/2 or lower), and on resistant and sensitive E. coli and S. aureus strains were observed some activities (Tables 5and 6). Surprisingly, on E. coli ATCC 25922 and S. aureus MRSA ATCC 43300, the essential

oil components -terpinene, terpinen-4-ol, sabinene, sabinene hydrate and linalool were effective biofilm formation inhibitors (inhibition 36–86%). In accordance with our findings, Kerekes et al. reported that O. majorana EO did not have inhibitory effect on biofilm formation, but their main components significantly inhibited the process in the case of Gram-positive bacteria (B. cereus) [29]. The Gram-negative bacteria biofilms (E. coli 0582) were inhibited by the EO, but the components were more effective. These results showed that the individual susceptibility of microbes is very different and plays a crucial role in the effectiveness of EOs and EO components [30]. The main target of these components is the cell wall and cytoplasmic membrane/or proteins embedded in the membrane

In biofilm formation assay on E. coli ATCC 25922 and S. aureus MRSA ATCC 43300, substantial inhibitory activity of the MeOH extract was observed (Tables 6 and 7). In the MeOH extract, the presence of phenolic acids, flavonoids, tannins, and triterpenes are expected and volatile compounds are in low concentration. The antibiofilm activity of the MeOH extract most probably can be explained by a high concentration of phenolic acids, rosmarinic acid, and chlorogenic acid [31]. Rosmarinic acid was reported to reduce biofilm formation of S. aureus in a concentration- and time-dependent manner in early-stage development [32]. RA also exerts inhibitory effects against E. coli K-12 and S. carnosus LTH1502 growth, through decreasing cell counts and cell numbers. The antibiofilm activity of chlorogenic acid against the clinical isolates of Stenotrophomonas maltophilia was displayed in vitro [33]. Other phenolic compounds, such as flavonoids, gallic acid, catechin may also have a contribution to antibiofilm activity [34].

Table 1. MIC values of the extracts and essential oil of O. majorana.

Samples	S. aureus ATCC 25923	S. aureus MRSA ATCC 43300	E. coli ATCC 25922	E. coli AG100
MeOH extract	>100 g/mL	>100 g/mL	>100 g/mL	>100 g/mL
n-hexane extract	>100 g/mL	>100 g/mL	>100 g/mL	>100 g/mL
Essential oil	0.125%	0.125%	0.125%	0.250%

Table 2. Minimum inhibitory concentrations (MICs) of O. majorana essential oil components.

Compounds	S. aureus ATCC 29213	S. aureus MRSA ATCC 43300	E. coli ATCC 35218	E. coli AG100
linalool	>10 L/mL >56 mM	>10 L/mL >56 mM	10 L/mL 56 mM	10 L/mL 56 mM
sabinene	10 L/mL >62 mM	10 L/mL >62 mM	>10 L/mL >62 mM	>10 L/mL >62 mM
sabinene-hydrate *	>0.154 mg/mL >62 mM	>0.154 mg/mL >62 mM	>0.154 mg/mL >62 mM	>0.154 mg/mL >62 mM
-terpinene	10 L/mL 61 mM	10 L/mL 61 mM	10 L/mL 61 mM	10 L/mL 61 mM
-terpinene	>10 L/mL >62 mM	>10 L/mL >62 mM	>10 L/mL >62 mM	>10 L/mL >62 mM
terpinen-4-ol	10 L/mL 60 mM	10 L/mL 60 mM	5 L/mL 30 mM	5 L/mL 30 mM

Table 3. Antibiofilm effect of extracts, essential oil of O. majorana and its monoterpene components on sensitive and resistant E. coli strains [1].

Sample	Inhibition %			
	E. coli ATCC 25922		E. coli AG100	
	0.0625%	0.0312%	0.125%	0.0625%
MeOH extract	5.77 **	**55.61 ***	59.60 ns	56.68 ns
n-hexane extract	**57.79 ***	**64.43** ns	13.74 *	41.58 **
Essential oil	104.64	–	**104.16**	–
	100 M/	50 M	100 M	50 M
-terpinene	1.95 *	17.68 **	53.71 ns	
-terpinene	**34.34 **	**37.80** *	33.37 ns	35.98 *
terpinene 4-ol	2.09 ***	**42.36** ns	28.19 ns	13.62 ns
sabinene	**36.35 **	**48.57** ns	59.78 ns	8.51 ns
sabinene hydrate	**37.93 ***	**55.97** *42.47 ns	12.13 *	15.40 ns
linalool	**28.98 ***	**49.68** ns	0.89 *	11.78 *
CCCP			**63.37**	

Table 4. Antibiofilm effect of extracts, essential oil of O. majorana and its monoterpene components on sensitive and resistant S. aureus strains [1].

Sample	Inhibition %			
	S. aureus ATCC 25923		S. aureus MRSA ATCC 43300	
	0.0625%	0.0312%	0.0625%	0.0312%
MeOH extract	0.93 **	1.93 **	**44.99 ** **	**39.69 ***
n-hexane extract	1.22 **	0.46 **	53.03 ns	18.37 **
Essential oil	**69.24**	–	4.38	–
	100 M	50 M	100 M	50 M
-terpinene	1.47 **	1.13 **	64.81 ns	26.82 **
-terpinene	0.76 **	1.91 ***	125.22 *	53.03 *
terpinene 4-ol	0.64 **	1.51 **	**66.31 ** **	**53.71 ** **
sabinene	0.61 **	1.83 ***	**53.53 ** **	**86.26 ***
sabinene hydrate	0.80 **	2.84 **	**60.56 ** **	**69.48 ** **
linalool	0.21 **	2.58 **	**34.44 ** **	**28.87 ***
DMSO	0.56		64.81	
TZ		**97.07**		**94.66**

1.2 Lavender

Biological name- *Lavandula angustifolia*

The Lamiaceae, or mint family, includes 47 species of flowering plants under the genus Lavandula, also known as lavender. It can be found in Cape Verde and the Canary Islands, as well as in northern and eastern Africa, the Mediterranean, southwest Asia, and India. It is a native of the Old World. [35]

Chemical Composition of Lavender Extracts

The essential oil (EO) of lavenders, which contains more than 50 mono- and sesquiterpene components, is particularly well-known. Linalool, linalyl acetate, borneol, and 1,8-cineole are the four major components of EO [36, 37]. Although plant health, meteorological season changes, harvest timing, post-harvest processing, and the method employed for essential oil extraction can all have an impact on oil composition, the precise constituent abundance (i.e., EO composition) is predominantly dictated by the species [38, 39–41]. Additionally, phenolic acids are accumulated by all Lavandula species, and these acids support the bioactivity of aqueous lavender extracts.

Drug Resistance effect

According to the result, a similar pattern of antimicrobial activity was observed in all of the isolates except P. aeruginosa. All P. aeruginosa isolates were resistant even to the highest concentration of EOL. The highest activity of EOL was observed at 1:1 dilution for other bacterial isolates. Bacterial sensitivity to EOL was found in the pattern of shrinking with the decreasing concentration. All P. mirabilis showed reduced susceptibility in 1:4 and 1:10 dilutions. Every A. hydrpohila and A. dhakensis isolates showed susceptibility against all tested concentrations of EOL. The maximumy inhibition zone was observed in A. dhakensis with 25 mm. Four out of eleven C. freundii and two out of six S. enterica were sensitive even in 1:10 dilution.

1.3 Silymarin-

Biological name- Silybum marianum

Plants and their derivatives have been employed as an alternative in the treatment of various ailments during the past few years [42]. Some writers have suggested using natural complementary therapies or even herbal extracts with hepatoprotective properties to lessen the liver damage caused by the treatment [43,44,45,46]. Hepatoprotective medications are frequently administered simultaneously with anti-TB therapy in nations like China [47,48,49]. A standardised extract of silymarin (Sm), which is obtained from the seeds of the milk thistle Silybum marianum and mostly made up of silibinin (Sb) (60–70%), silydianin, and silychristin, is one of the most popular therapies for liver problems. [50]

Drug resistance effect -

Anti-TB medications are often a successful kind of therapy. They could, however, have negative effects [51, 52]. Long-term administration of INH and RIF can cause liver malfunction and damage due to a significant production of oxygen free radicals [53]. Therefore, it's critical to find shorter, less harmful treatment plans [54,55] that can also be utilised as preventative medicine [56]. In the hunt for novel medications with antibacterial [57,58], antioxidant [59], or hepatoprotective actions to treat the steadily rising numbers of patients of MDR and XDR TB, natural products provide a compelling option. With a standardised extract from Sm, this is the situation.

Additionally, studies on Sm have demonstrated that it has immunoregulatory [60], anti-inflammatory [61], and antioxidant effects [62]. Regarding the immunoregulatory actions, Sm favours the TH2 immunological pattern by polarising the immune response in a dose-dependent manner [63]. Sm inhibits the NF-B pathway in particular cells like mast cells and increases TGF-1 expression (which contributes to its anti-inflammatory properties) [64,65]. It also lowers the lipoxygenase pathway in Kupffer cells, which affects prostaglandin release and leukotriene synthesis [66]. All these effects are detrimental to TB immune defence because it is well known that Th-1 and activated macrophages that actively create NO and oxygen free radicals are necessary to eradicate mycobacteria in people and animals [67,68,69].

Finally, it was investigated if a flavonoid derived from plants could be used alone or in combination with anti-TB medications. Our in vitro and in vivo experiments revealed that Sm decreased mycobacterium viability and increased the expression of the proinflammatory cytokines TNF- and IFN-, favouring a TH1 immune response that significantly aided in the management of infections caused by both drug-sensitive and drug-resistant mycobacteria.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

REFERENCES

[1] Livermore DM. Has the era of untreatable infections arrived? J Antimicrob Chemother 2009;64(Suppl. 1). i29e36.

[2] Kalan L, Wright GD. Antibiotic adjuvants: multicomponent anti-infective strategies. Expert Rev Mol Med 2011;13:e5.

[3] Cohen, M.L. Epidemiology of drug resistance: implications for a postantimicrobial era. Science 257, 1050-1055, 1992.

[4] Montelli, A.C.; Levy, C.E.. Sistema COBA - Aspectos relativos aos dados dos laboratórios de referência. Rev. Microbiol. 22, 197-205, 1991

[5] Santos, P.R.V.; Oliveira, A.C.X.; Tomassini, T.C.B. Controle microbiógico de produtos fitoterápicos. Rev. Farm. Bioquím. 31, 35-38, 1995.

[6] . Ellof, J.N. Which extractant should be used for the screening and isolation of antimicrobial components from plants? J. Ethnopharmacol. 60, 1-6, 1998.

[7] Schelz Z, Molnar J, Hohmann J. Antimicrobial and antiplasmid activities of essential oils. Fitoterapia 2006; 77(4): 279-285.

[8] Prabuseenivasan S, Jayakumar M, Ignacimuthu S. In vitro antibacterial activity of some plant essential oils. BMC Complement Altern Med 2006; 6: 39.

[9] O'Bryan CA, Pendleton SJ, Crandall PG, Ricke SC. Potential of Plant Essential Oils and Their Components in Animal Agriculture-in vitro Studies on Antibacterial Mode of Action. Front Vet Sci 2015; 2: 35.

[10] Andersson DI, Hughes D. Persistence of antibiotic resistance in bacterial populations. FEMS Microbiol Rev 2011;35:901e11.

[11] Stabili L, Acquaviva MI, Biandolino F, Cavallo RA, De Pascali SA, et al. The lipidic extract of the seaweed Gracilariopsis longissima (Rhodophyta, Gracilariales): a potential resource for biotechnological purposes? New Biotechnol 2012;29:443e50.

[12] Cavanagh HMA, Wilkinson JM. Lavender essential oil: A review. Aust Infect Control 2005; 10(1): 35-37.

[13] Sienkiewicz M, Głowacka A, Kowalczyk E, WiktorowskaOwczarek A, Jóźwiak-Bębenista M, Łysakowska M. The biological activities of cinnamon, geranium and lavender essential oils. Molecules 2014; 19(12): 20929-20940.

[14] E. Vagi, B. Simándi, H. Daood, A. Deak, J. Sawinsky. (2002). Recovery of pigments from Origanum majorana L. by extraction with supercritical carbon dioxide. Journal of agricultural and food chemistry. 50(8): 2297-2301.

[15] L. Faleiro, G. Miguel, S. Gomes, L. Costa, F. Venâncio, A. Teixeira, A.C. Figueiredo, J.G. Barroso, L.G. Pedro. (2005). Anti-bacterial and anti-oxidant activities of essential oils isolated from Thymbra capitata L.(Cav.) and Origanum vulgare L. Journal of agricultural and food chemistry. 53(21): 8162-8168.

[16] K. Bauer, D. Garbe, H. Surburg. (2008). Common fragrance and flavor materials: preparation, properties and uses. John Wiley & Sons: pp.

[17] J. Novak, J. Langbehn, F. Pank, C.M. Franz. (2002). Essential oil compounds in a historical sample of marjoram (Origanum majorana L., Lamiaceae). Flavour and fragrance journal. 17(3): 175-180.

[18] M.T. Baratta, H. Dorman, S.G. Deans, A.C. Figueiredo, J.G. Barroso, G. Ruberto. (1998). Antimicrobial and anti-oxidant properties of some commercial essential oils. Flavour and fragrance journal. 13(4): 235-244.

[19] J.A. Pino, A. Rosado, M. Estarrón, V. Fuentes. (1997). Essential oil of Majoram (Origanum majorana L.) grown in Cuba. Journal of Essential Oil Research. 9(4): 479-480.

[20] M.T. Baratta, H. Dorman, S.G. Deans, A.C. Figueiredo, J.G. Barroso, G. Ruberto. (1998). Antimicrobial and anti-oxidant properties of some commercial essential oils. Flavour and fragrance journal. 13(4): 235-244

[21] W.J. Jun, B.K. Han, K.W. Yu, M.S. Kim, I.S. Chang, H.Y. Kim, H.Y. Cho. (2001). Anti-oxidant effects of Origanum majorana L. on superoxide anion radicals. Food Chemistry. 75(4): 439-444

[22] Nové, M.; Kincses, A.; Szalontai, B.; Rácz, B.; Blair, J.M.A.; González-Prádena, A.; Benito-Lama, M.; Domínguez-Álvarez, E.; Spengler, G. Biofilm Eradication by Symmetrical Selenoesters for Food-Borne Pathogens. Microorganisms **2020**, 8, 566. [CrossRef]

[23] Zeouk, I.; Lalami, A.E.O.; Bekhti, K. In Vitro Antibacterial Activity of Medicinal Plants in the Central North of Morocco: A Possible Source of Alternative Drugs against Methicillin-Resistant Staphylococcus aureus. Asian J. Pharm. Clin. Res. **2019**, 12, 285–292

[24] Carson, C.F.; Riley, T.V. Antimicrobial Activity of the Major Components of the Essential Oil of Melaleuca alternifolia. J. Appl. Bacteriol. **1995**, 78, 264–269. [CrossRef]

[25] Cordeiro, L.; Figueiredo, P.; Souza, H.; Sousa, A.; Andrade-Júnior, F.; Medeiros, D.; Nóbrega, J.; Silva, D.; Martins, E.; Barbosa-Filho, J.; et al. Terpinen-4-ol as an Antibacterial and Antibiofilm Agent against Staphylococcus aureus. Int. J. Mol. Sci. **2020**, 21, 4531.

[26] Szemerédi, N.; Kincses, A.; Rehorova, K.; Hoang, L.; Salardón-Jiménez, N.; Sevilla-Hernández, C.; Viktorová, J.; Domínguez-Álvarez, E.; Spengler, G. Ketone- and Cyano-Selenoesters to Overcome Efflux Pump, Quorum-Sensing, and Biofilm-Mediated Resistance. Antibiotics **2020**, 9, 896.

[27] Yoshida, N.; Koizumi, M.; Adachi, I.; Kawakami, J. Inhibition of P-Glycoprotein-Mediated Transport by Terpenoids Contained in Herbal Medicines and Natural Products. Food Chem. Toxicol. **2006**, 44, 2033–2039.

[28] Kincses, A.; Szabó, S.; Rácz, B.; Szemerédi, N.; Watanabe, G.; Saijo, R.; Sekiya, H.; Tamai, E.; Molnár, J.; Kawase, M.; et al. Benzoxazole-Based Metal Complexes to Reverse Multidrug Resistance in Bacteria. Antibiotics **2020**, 9, 649.

[29] Kerekes, E.B.; Deák, É.; Takó, M.; Tserennadmid, R.; Petkovits, T.; Vágvölgyi, C.; Krisch, J. Anti-Biofilm Forming and Anti-Quorum Sensing Activity of Selected Essential Oils and their Main Components on Food-Related Microorganisms. J. Appl. Microbiol. **2013**, 115, 933–942.

[30] Rossi, C.; Chaves-López, C.; Serio, A.; Casaccia, M.; Maggio, F.; Paparella, A. Effectiveness and Mechanisms of Essential Oils for Biofilm Control on Food-Contact Surfaces: An Updated Review. Crit. Rev. Food Sci. Nutr. **2022**, 62, 2172–2191.

[31] Duleti´c-Lauševi´c, S.; Aradski, A.A.; Kolarevi´c, S.; Vukovi´c-Gaˇci´c, B.; Oalde,¯ M.; Živkovi´c, J.; Šavikin, K.; Marin, P.D. Antineurode-generative, Antioxidant and Antibacterial Activities and Phenolic Components of Origanum majorana L. (Lamiaceae) Extracts. J. Appl. Bot. Food Qual. **2018**, 91, 126–134.

[32] Slobodníková, L.; Fialová, S.; Hupková, H.; Granˇcai, D. Rosmarinic Acid Interaction with Planktonic and Biofilm Staphylococcus aureus. Nat. Prod. Commun. **2013**, 8, 1747–1750.

[33] Karunanidhi, A.; Thomas, R.; van Belkum, A.; Neela, V. In Vitro Antibacterial and Antibiofilm Activities of Chlorogenic Acid against Clinical Isolates of Stenotrophomonas maltophilia including the Trimethoprim/Sulfamethoxazole Resistant Strain. Biomed. Res. Int. **2013**, 2013, 392058. [CrossRef]

[34] Slobodníková, L.; Fialová, S.; Rendeková, K.; Kovác,ˇ J.; Muˇcaji, P. Antibiofilm Activity of Plant Polyphenols. Molecules **2016**, 21, 1717. [CrossRef]

[35] Outdoor flowering plants – mona lavender *www.hgtv.com. HGTV*. Retrieved 19 October 2018

[36] Śmigielski KZ, Prusinowska R, Krosowiak K, Sikora M. (**2013**) Comparison of qualitative and quantitative chemical composition of hydrolate and essential oils of lavender (lavandula angustifolia). Journal of Essential Oil Research, 25, 291–299.

[37] Lis-Balchin M. (**2002**) Lavender: *The genus Lavandula.* (1st ed.). Taylor and Francis Inc New

a. York, NY.

[38] Danh LT, Triet NDA, Han LTN, Zhao J, Mammucari R, Foster N. (**2012**) Antioxidant activity, yield and chemical composition of lavenderessential oil extracted by supercritical CO2. *The Journal of Supercritical Fluids*, ***70***, 27–34.
[39] Ghoreishi SM, Kamali H, Ghaziaskar HS, Dadkhah AA. (**2012**) Optimization of Supercritical extraction of linalyl acetate from lavender via box- behnken design. *Chemical Engineering & Technology*, ***35***, 1641-1648.
[40] Kamali H, Aminimoghadamfarouj N, Golmakani E, Nematollahi A. (**2014**) The optimization of essential oils supercritical CO2 extraction from *lavandula* hybrida through static-dynamic steps procedure and semi-continuous technique using response surface method. *Pharmacognosy Research*, ***7***, 57–65.
[41] Zheljazkov VD, Astatkie T, Hristov AN. (2012) Lavender and hyssop productivity, oil content, and bioactivity as a function of harvest time and drying. *Industrial Crops & Products*, *36*, 222–228.
[42] Zheljazkov VD, Cantrell CL, Astatkie T, Jeliazkova E. (2013) Distillation time effect on lavender essential oil yield and composition. Journal of Oleo Science, 62, 195–199.
[43] de Oliveira DR, Tintino SR, Braga MF, Boligon AA, Athayde ML, Coutinho HD, et al. In vitro antimicrobial and modulatory activity
[44] Garcı´a A, Bocanegra-Garcı´a V, Palma-Nicola´s JP, Rivera G. Recent advances in antitubercular natural products. Eur J Med Chem. 2012 Mar; 49:1–23 https://doi.org/10.1016/j.ejmech.2011.12.029 PMID: 22280816
[45] Keri RS, Sasidhar BS, Nagaraja BM, Santos MA. Recent progess in the drug development of coumarin derivates as potent antituberculosis agents. Eur J Med Chem. 2015; 100: 257–69 https://doi.org/10. 1016/j.ejmech.2015.06.017 PMID: 26112067
[46] Lee H, Suh JW. Anti-tubercular lead molecules from natural products targeting Mycobacterium tuberculosis ClpC1. J Ind Microbiol Biotechnol. 2016; 43 (2–3): 205–12 https://doi.org/10.1007/s10295-015- 1709-3 PMID: 26586403
[47] Oosthuizen C, Arbach M, Meyer D, Hamilton C, Lall N. Diallyl Polysulfides from Allium sativum as Immunomodulators, Hepatoprotectors, and Antimycobacterial Agents. J Med Food. 2017 Apr 14
[48] Jiang RH, Xu HB, Fu J. Outcomes of Chinese herb medicine for the treatment of multidrug-resistant tuberculosis: a systematic review and meta-analysis. Complement Ther Med. 2015. 23(4):544–54 https://doi.org/10.1016/j.ctim.2015.06.006 PMID: 26275647
[49] Wu S, Xia Y, Lv X, Tang S, Yang Z, Zhang Y, et al. Preventive use of hepatoprotectors yields limited efficacy on the liver toxicity of anti-tuberculosis agents in a large cohort of Chinese patients. J Gastroenterol Hepatol. 2015. 30:540–545 https://doi.org/10.1111/jgh.12717 PMID: 25160904
[50] Zhang S, Pan H, Peng X, Lu H, Fan H, Zheng X, et al. Preventive use of a hepatoprotectant against anti-tuberculosis drug-induced liver injury: A randomized controlled trial. J Gastroenterol Hepatol. 2016. 31:409–416 https://doi.org/10.1111/jgh.13070 PMID: 26243373
[51] Abenavoli L, Capasso R, Milic N, Capasso F. Milk thistle in liver diseases: past, present, future. Phytother Res. 2010. 24:1423–1432 https://doi.org/10.1002/ptr.3207 PMID: 20564545
[52] Lima MM, Trindade A, Carnavalli F, Bolognesi-Melchio AC, Chin CM, Dos Santos JL. Tuberculosis: Challenges to improve the treatment. Curr Clin Pharcacol. 2015; 10 (3): 242–51
[53] Rennie RP. Current and future challenges in the development of antimicrobial agents. Handb Exp Pharmacol. 2012.(211):45–65 https://doi.org/10.1007/978-3-642-28951-4_4 PMID: 23090595
[54] Sonika U, Kar P. Tuberculosis and liver disease: management issues. Trop Gastroenterol 2012. 33:102–106 PMID: 23025055
[55] Dooley KE, Phillips PP, Nahid P, Hoelscher M. Challenges in the clinical assessment of novel tuberculosis drugs. Adv Drug Deliv Rev. 2016. 102:116–https://doi.org/10.1016/j.addr.2016.01.014 PMID: 26827911
[56] Hoagland DT, Liu J, Lee RB, Lee RE. New agents for the treatment of drug-resistant Mycobacterium tuberculosis. Adv Drug
[57] Garcıa A, Bocanegra-Garcı´a V, Palma-Nicola´s JP, Rivera G. Recent advances in antitubercular natural products. Eur J Med Chem. 2012 Mar; 49:1–23 https://doi.org/10.1016/j.ejmech.2011.12.029 PMID: 22280816
[58] Mascarello A, Chiaradia- Delatorre LD, Mori M, Terenzi H, Botta B. Mycobacterium tuberculosis secreted tyrosine phosphatases as targets agains tuberculosis: Exploring Natural Sources in searching for New Drugs. Curr Pharm Des. 2016; 22 (12): 1561–9 PMID: 26759082
[59] Salomon CE, Schmidt LE. Natural products as leads for tuberculosis drug development. Curr Top Med Chem 2012. 12:735–765 PMID: 2228381

[60] Gharagozloo M, Jafari S, Esmaeil N, Javid EN, Bagherpour B, Rezaei A. Immunosuppressive effect of silymarin on mitogen-activated protein kinase signalling pathway: the impact on T cell proliferation and cytokine production. Basic Clin Pharmacol Toxicol. 2013. 113:209–214 https://doi.org/10.1111/bcpt.12088 PMID: 23701595
[61] 1111/j.1365-2125.1987.tb03241.x PMID: 2449903 34. Manna SK, Mukhopadhyay A, Van NT, Aggarwal BB. Silymarin suppresses TNF-induced activation of NF-kappa B, c-Jun N-terminal kinase, and apoptosis. J Immunol 1999. 163:6800–6809 PMID: 10586080
[62] Surai PF. Silymarin as a Natural Antioxidant: An Overview of the Current Evidence and Perspectives. Antioxidants (Basel). 2015. 4:204–247
[63] Casas-Grajales S, Muriel P. Antioxidants in liver health. World J Gastrointest Pharmacol Ther. 2015. 6:59–72. PMID: 26261734
[64] Lee JS, Kim SG, Kim HK, Lee TH, Jeong YI, Lee CM, et al. Silibinin polarizes Th1/Th2 immune responses through the inhibition of immunostimulatory function of dendritic cells. J Cell Physiol. 2007. 210:385–397 https://doi.org/10.1002/jcp.20852 PMID: 17058260
[65] Kim EJ, Lee MY, Jeon YJ. Silymarin Inhibits Morphological Changes in LPS-Stimulated Macrophages by Blocking NF-kappaB Pathway. Korean J Physiol Pharmacol 2015. 19:211–218 https://doi.org/10.4196/kjpp.2015.19.3.211 PMID: 25954125
[66] Jeong DH, Lee GP, Jeong WI, Do SH, Yang HJ, Yuan DW, et al. Alterations of mast cells and TGFbeta1 on the silymarin treatment for CCl(4)-induced hepatic fibrosis. World J Gastroenterol. 2005. 11:1141–1148 https://doi.org/10.3748/wjg.v11.i8.1141 PMID: 15754394
[67] Raso GM, Meli R, Di Carlo G, Pacilio M, Di Carlo R. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1. Life Sci 2001. 68:921–931 PMID: 11213362
[68] Abate G and Hoft D. Immunotherapy for tuberculosis: future prospects. ImmunoTargets and Therapy. 2016. 5:37–45 https://doi.org/10.2147/ITT.S81892 PMID: 27529060
[69] Nairz M, Dichtl S, Schroll A, Haschka D, Tymoszuk P, Theurl I, et al. Iron and innate antimicrobial immunity-Depriving the pathogen, defending the host. J Trace Elem Med Biol. 2018 Jul; 48:118–133 https:// doi.org/10.1016/j.jtemb.2018.03.007 PMID: 29773170