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Antimicrobial Synergism within Plant Extract Combinations

Alqudah AA*

Department of applied Biology, Tafila Technical University, Jordan

***Corresponding author:** Ali Abdallah Alqudah, Department of applied Biology, Faculty of Science, Tafila Technical University, Jordan, Email: ali_quda@yahoo.com

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Abstract

Ideas for research are drawn from the herbal medicine tradition of synergy. Using online databases, a study of the literature on plant synergy and antimicrobial research that was published in most recent years. In each plant sample, the efficacies of the various extract combinations varied, with some combinations of plant extracts exhibiting the greatest synergistic effects when combined according to proportionate extract yield. Since the beginning of time, herbal medicines and phytochemicals have been employed for their potent antibacterial action, and there is a growing trend toward the creation of plant-based natural products for the prevention and treatment of pathogenic infections. Utilizing antimicrobial agent-phytochemical combinations to neutralize the resistance mechanism and maintain the drug's efficacy against resistant microorganisms is one method for successfully modifying resistance.

Keywords: Synergy; Antimicrobial; Plant

Introduction

Plants have been used for medicinal purposes long before prehistoric period and represent the most ancient form of medication. Ancient Unani manuscripts, Egyptian papyrus and Chinese writings described the use of herbs. Plant used for thousands of years in traditional medicine in many countries around the world [1,2]. Most of the beneficial knowledge about their valuable effects was transferred over the centuries within human communities. Evidence from previous cultures like Indian, European, and Mediterranean have been using herbs for over 4000 years as medicine. Indigenous cultures such as Rome, Egypt, Iran, Africa, and America used herbs in their healing rituals [3,4].

Nowadays, using of medicinal plant remains widespread, and plays a significant role of the world's population herbal natural cures and supplements as the primary mode of healthcare. The World Health Organization stated that 80% of people in developing countries still rely on traditional medicine and utilize botanical supplements to treat disease [5,6]. Plants consider as a valuable source of medicines because they provide a lot of bioactive molecules. Most of these molecules work as a chemical defence mechanism against infection and herbivores [7-9].

Historically, plants have provided a source of inspiration for novel drugs and have made large contributions to human health and well-being. Natural products have served as a major source of drugs for centuries and about 25—50% of current pharmaceuticals in use are derived from natural products [10,11]. Medicinal plant extracts were reported for their anti-inflammatory [12-14], antibacterial [15,16], antifungal [17,18], and antiviral activities [19]. The interaction between antimicrobials in a combination can have three different outcomes, synergistic, additive, or antagonistic. Synergy occurs when a blend of two antimicrobial compounds has an antimicrobial activity that is greater than the sum of the individual components. An additive effect is obtained when the combination of antimicrobials has a combined effect equal to the sum of the individual compounds. Antagonism occurs when a blend of antimicrobial compounds has a combined effect less than when applied separately [20,21]. This review aims to provide practical advice to investigators seeking to comprehensively evaluate the constituents and mechanisms responsible for the biological activity of botanical mixtures.

Antimicrobial Resistance

Some of the oldest life forms, bacteria are prokaryotic microorganisms that helped to build a world that is hospitable to animal life. Since the eighteenth century, there have been disagreements over whether environmental factors or microorganisms are to blame for the development of diseases [22,23]. Antimicrobial resistance (AMR) is a pressing global health concern that poses a significant threat to our ability to treat infections effectively. It refers to the ability of microorganisms, such as bacteria, viruses, and parasites, to evolve and develop resistance to the drugs designed to kill or inhibit their growth. This phenomenon is primarily caused by the overuse and misuse of antimicrobial drugs in humans, animals, and agriculture [24,25]. The consequences of AMR are far-reaching, as it can render once-effective antibiotics and other antimicrobial treatments ineffective, leading to prolonged illnesses, increased mortality rates, and higher healthcare costs [26]. To combat this growing problem, it is crucial to promote responsible use of antibiotics, develop new antimicrobial agents, enhance surveillance and monitoring systems, and educate healthcare professionals and the public about the appropriate use of these life-saving drugs [27]. Addressing antimicrobial resistance requires a coordinated global effort to preserve the effectiveness of existing treatments and safeguard future generations against the threat of untreatable infections [26]. Antibiotic resistance is becoming more and more widely recognized as a threat to public health, as is the rise in antibiotic resistance among bacteria that are significant human pathogens and the spread of resistance from the relatively closed environment of hospitals into open communities [28]. The development of multi-drug resistance or combinations of resistance, the emergence of new resistance mechanisms, and the ease with which genetic material encoding resistance may, in some circumstances, spread horizontally between different species of bacteria all contribute to a greater sense of helplessness against diseases that, when antibiotics were first invented, were believed to be under control [29,30].

Bacteria have evolved and developed new bacterial resistance mechanisms in order to live due to a number of circumstances, including overuse of antibiotics in agricultural and healthcare [31]. Although thoroughly documented, it is still unclear how using a single antibiotic for just two weeks might cause bacteria in a human or animal body to become multidrug resistant (MDR) [32-34]. When bacteria resist one treatment, “it is almost as if they strategically anticipate the confrontation of other drugs” [33]. According to Smillie CS, et al. [34], horizontal genetic transfer of mobile characteristics is thought to be the cause of the startlingly large amount of transferable drug resistance between various species of bacteria. The Human Microbiome Project’s director, Blaser MJ, et al. [32], explains how a species’ microbiome is made up of the trillions of bacteria that have co-evolved to coexist with it. According to Blaser MJ, et al. [32], microbial symbionts make up 70–90% of human body cells and perform a variety of crucial metabolic and defensive tasks.

Plant Secondary Metabolites

Plant secondary metabolites, also known as phytochemicals, are organic compounds that are not directly involved in the essential functions of plant growth and development but play significant roles in plant defense mechanisms and interactions with the environment [35]. These compounds are produced by plants through various biochemical pathways and are often concentrated in specific plant tissues or organs, such as leaves, flowers, fruits, and roots [36,37].

Plant secondary metabolites have diverse chemical structures and functions. They serve as defense mechanisms against herbivores, pests, and pathogens by deterring or repelling them, or by inhibiting their growth and development. Some secondary metabolites, such as alkaloids, phenolics, and terpenoids, have antimicrobial properties and can help plants combat infections [38-40]. The treatment of infections and health disorders with herbal medicines is usually involves active natural products mostly of low molecular weight of great structural diversity [41,42]. More than 200,000 defined structures of plant secondary metabolites have been known. Some plants or their extracts with high concentrations of bioactive plant secondary metabolites such as saponins, tannins, essential oils, organosulphur compounds, flavonoids and many other metabolites have potential to treat many diseases [38]. Many scientific sources state that their role is not crucial for living cells in normal growth, development, and reproduction, but they act in defensive purposes to protect a plant from any possible harm in the ecological environment and other interspecies protection [43]. Many scientific sources state that while they serve defensive functions to protect the plant from potential harm in the ecological environment and other interspecies protection, their role is not essential for plant physiology in normal growth, development, and reproduction [40]. Consequently, they are typically produced in plants to meet specific needs, whereas primary metabolites typically serve the crucial biological functions in all species [44]. Secondary metabolites produced by modified synthetic pathways from primary metabolite or share substrates of primary metabolite origin [45]. To adapt to their environment, plants have been genetically encoding a variety of helpful synthases for secondary metabolites. These substances, particularly essential oils, are utilized as medications, flavors, or sedatives in human life [46]. In most recent references, secondary metabolites extracted from plants are subdivided in three major classes: terpenoids, alkaloids and phenolics. They contain a huge number of organic compounds with intriguing pharmacological properties [38]. Here are a few examples of plant secondary metabolites and their association with specific diseases:

- Flavonoids: Flavonoids are a class of secondary metabolites found abundantly in fruits, vegetables, and herbs. They possess antioxidant and anti-inflammatory properties [47-49], which make them beneficial in combating chronic diseases such as cardiovascular diseases [50], cancer [51,52], and neurodegenerative disorders [53].
- Alkaloids: Alkaloids are a diverse group of secondary metabolites that exhibit a wide range of pharmacological activities. For instance, alkaloids like vincristine and vinblastine from the Madagascar periwinkle (Catharanthus roseus) have been used as chemotherapy agents for the treatment of cancer [54]. Also, the anticholinesterase activity of alkaloids, together with their structural diversity and physicochemical properties, makes them good candidate agents for the treatment of Alzheimer's disease [55].
- Terpenoids: Terpenoids, including essential oils, have been extensively studied for their antimicrobial [56], anti-inflammatory [57], and anticancer activities [58,59]. Examples include the antimalarial drug artemisinin derived from Artemisia annua and the anticancer drug paclitaxel derived from Taxus brevifolia [60].
- Phenolic compounds: Phenolic compounds, such as resveratrol found in grapes and berries, have shown potential in protecting against cardiovascular diseases and cancer [61]. They possess antioxidant properties and can help reduce oxidative stress and inflammation in the body [62,63]. These compounds have been investigated for their potential role in preventing or treating various diseases, such as diabetes [64], cancer [65], cardiovascular diseases [66] and neurodegenerative disorders [67].
- Glycosides: Plant glycosides have been investigated for their effects on various health conditions. For instance, cardiac glycosides derived from plants like Digitalis purpurea have been used to treat heart failure and certain arrhythmias [68-70].

It's important to note that while plant secondary metabolites offer promising therapeutic potential, their efficacy and safety need to be further studied and validated through rigorous scientific research and clinical trials. Additionally, the appropriate dosage, administration, and potential interactions with medications should be carefully considered when utilizing plant secondary metabolites for disease prevention or treatment.

Development of Synergistic Effects of Plant Extracts

According to the presumption that a plant has one or a few chemicals that influence its medicinal effects, many scientists have focused for decades primarily on the search for the single active component in plants. But traditional systems of medicines like European phytotherapy and traditional Chinese Medicine assume that a synergy of all ingredients of the plants will result in the greatest medicinal efficacy [71]. Due to the lack of sufficient methods to standardize complex plant mixtures (as medications) and to explain the complicated mode of activities, this approach has long been impossible to research. The recent advancements in synergy research have opened highly interesting perspectives for a new generation of phytopharmaceuticals. The emergence and rapid shift in chemotherapy, involving the gradual change from the mono-substance therapy to a multidrug therapy with high efficiency [72,73]. This is mostly due to the ineffectiveness, resistance issues, and potential side effects of synthetic mono-drugs, particularly when used to treat chronic conditions such as diabetes, cancer, inflammation, and atherosclerosis. The rationale behind employing multiple drug therapy for various disorders is the recognition that for each, more than one mechanism and gene is identified [74]. For instance, the pathway components that are altered in any individual tumor vary widely [75]. In addition, 12 partially overlapping processes that are genetically changed in the vast majority of pancreatic tumors have been identified by a global genomic investigation [76]. The complex multi-component character of medicinal herbs may serve as a rich resource for network-based multi-target drug discovery due to its potential therapeutic benefits by synergy. Herb extracts are complex combinations of main chemicals, concurrent drugs, and other substances [77]. Recently, Epigallocatechin gallate (EGCG), is able to increase the therapeutic effectiveness of temozolomide in patients with glioblastoma [78]. The EGCG can cross the blood–brain barrier to cause chemosensitization in a mouse glioma model. When the EGCG combined with temozolomide, the expression levels of glucose-regulated protein 78 in temozolomide-treated animals were reduced significantly, which plays a crucial role in pro-survival component of the endoplasmic reticulum stress response system (EGCG alone did not have any survival-enhancing effects) [79].

Synergistic Effect of Combinations of Herbal Extracts

Combining different plant extracts with various bioactive components has been shown to result in either synergistic or antagonistic effects in their bioactive effects. Synergistic effects can occur when the extracts of two or more plant species exhibit greater effects than the extracts of one plant species. Malongane F, et al. [80] found the common bioactive compounds mainly in green teas are flavan-3-ols (catechins), proanthocyanidins, flavonols and Black tea contains theaflavins and thearubigins and white tea contains L-theanine and gamma-aminobutyric acid (GABA), while herbal teas contain diverse polyphenols. All these phytochemicals in tea exhibit antimicrobial, anti-diabetic and anti-cancer activities that are perceived to be helpful in managing chronic diseases linked to lifestyle. Many of these phytochemicals are reported to be biologically active when combined. In a study achieved by Nuria I. Guardo, et al., 2017, fourteen essential oils (EOs) from selected live germplasm of medicinal plants have been tested for their antitrypanosomal and cytotoxic activity. And the study of the activity of these compounds in combination indicates the existence of synergistic effects depending on the concentration tested.

Antimicrobial Research and Plant Synergy

Research on the antimicrobial properties of plants and the potential synergistic effects of combining plant components has gained significant attention due to the increasing problem of antimicrobial resistance. Here are some aspects of recent studies on antimicrobial research and plant synergy:

- Synergistic Combinations: Researchers have been investigating the combined effects of different plant extracts, essential oils, or phytochemicals to enhance their antimicrobial activity. Studies have explored combinations of plant extracts with known antimicrobial properties, such as tea tree oil, cinnamon oil, and oregano oil, and demonstrated enhanced effectiveness against various pathogens [81-83]. For example, a study published in the Journal of Applied Microbiology found that a combination of thyme and cinnamon essential oils showed synergistic activity against antibiotic-resistant bacteria [84].
- Mechanisms of Action: Researchers are also investigating the mechanisms by which plant compounds exert their antimicrobial effects and whether combining different compounds can have additive or synergistic effects. Studies have explored the interactions between different phytochemicals and their impact on disrupting bacterial cell membranes, inhibiting enzyme activity, or interfering with microbial biofilms [85,86].
- Plant-Drug Combinations: Some studies have focused on the potential synergistic effects of combining plant extracts or phytochemicals with conventional antibiotics [87,88]. The goal is to enhance the effectiveness of existing antimicrobial drugs and potentially reduce the required dosage, thus minimizing the development of drug resistance. For instance, a study published in the Journal of Ethnopharmacology investigated the synergistic effects of combining the antibiotic gentamicin with various plant extracts, showing enhanced antibacterial activity against multidrug-resistant strains [89].
- Combination Therapy Against Biofilms: Biofilms are complex microbial communities that are highly resistant to antimicrobial agents. Researchers are exploring the use of plant extracts or phytochemical combinations to disrupt biofilms and enhance the efficacy of antimicrobial treatments. Studies have shown promising results in using plant-based formulations to target biofilms of various pathogens, including bacteria and fungi [90,91].
- Identification of Active Compounds: Advances in analytical techniques and screening methods have allowed for the identification of specific active compounds responsible for the antimicrobial effects of plants. Researchers are isolating and characterizing these compounds and investigating their interactions and potential synergistic effects when combined [92,93].

It's important to note that while these studies show promising results, further research is needed to fully understand the mechanisms and optimize the use of plant synergy in antimicrobial applications. Additionally, evaluating safety, dosage, and potential interactions with other medications is crucial for the development of effective and safe antimicrobial therapies.

Studies on Plant Synergistic Effect

Research on plant synergistic effects is a dynamic field with numerous studies exploring the combined effects of different plant components. Here are a few examples of studies conducted on plant synergistic effects:

- Curcumin and Piperine: Curcumin, a bioactive compound found in turmeric, has shown various health benefits. However, its bioavailability is limited [94,95]. Several studies have investigated the synergistic effect of combining curcumin with piperine, a compound derived from black pepper. Piperine has been found to enhance the absorption and bioavailability of curcumin, leading to improved therapeutic effects [96-98].
- Green Tea and Citrus Flavonoids: Green tea is known for its antioxidant properties, while citrus fruits are rich in flavonoids [99]. A study published in the Journal of Nutrition demonstrated that combining green tea catechins with citrus flavonoids resulted in a synergistic effect, leading to enhanced antioxidant activity and

protection against oxidative stress [80,100].

- Garlic and Onions: Garlic and onions are both rich in organosulfur compounds, which have antimicrobial and anticancer properties. Studies have indicated that the combination of garlic and onions may exhibit a synergistic effect in inhibiting the growth of cancer cells and enhancing the overall anticancer activity compared to using each ingredient individually [101].
- Herbal Combinations in Traditional Medicine: Traditional medicine systems, such as Ayurveda and Traditional Chinese Medicine, often utilize combinations of multiple herbs to treat various ailments. Numerous studies have investigated the synergistic effects of herbal combinations and found that certain combinations exhibit enhanced therapeutic effects compared to individual herbs alone. For example, a study published in the Journal of Ethnopharmacology found that a combination of three herbs used in traditional Ayurvedic medicine showed stronger antidiabetic activity than when each herb was used separately [102,103].
- Essential Oils: Essential oils derived from different plant sources often consist of a complex mixture of compounds. Research has focused on studying the synergistic effects of these compounds. For instance, a study published in the Journal of Agricultural and Food Chemistry explored the synergistic antimicrobial effects of essential oil components from oregano, thyme, and clove against foodborne pathogens, demonstrating enhanced antimicrobial activity when the compounds were combined [104,105].

These are several examples of the studies conducted on plant synergistic effects. Researchers continue to explore and unravel the interactions between plant components, aiming to optimize the therapeutic potential of plants and develop effective combination therapies for various applications.

References

1. Sengupta G, Gaurav A, Tiwari S (2018) Substituting medicinal plants through drug synthesis. Synthesis of Medicinal Agents from Plants pp: 47-74.
2. Halberstein RA (2005) Medicinal plants: historical and cross-cultural usage patterns. Annals of Epidemiology 15(9): 686-699.
3. Awuchi CG (2019) Medicinal plants: the medical, food, and nutritional biochemistry and uses. International Journal of Advanced Academic Research 5(11): 220-241.
4. Shaheen S, Ramzan S, Khan F, Ahmad M, Shaheen S, et al. (2019) Why Study Herbal Plants. In: Shaheen S, et al. (Eds.), Adulteration in Herbal Drugs A Burning Issue, Springer, Cham, pp: 17-33.
5. Bhardwaj S, Verma R, Gupta J (2018) Challenges and future prospects of herbal medicine. International Research in Medical and Health Sciences 1(1): 12-15.
6. Khan MSA, Ahmad I (2019) Herbal medicine: current trends and future prospects. In: Ahmad I, et al. New look to phytomedicine. Elsevier, pp: 3-13.
7. Buchel K, Fenning T, Gershenzon J, Hilker M, Meiners T, et al. (2016) Elm defence against herbivores and pathogens: morphological, chemical and molecular regulation aspects. Phytochemistry Reviews 15: 961-983.
8. War AR, Paulraj MG, Ahmad T, Buhroo AA, Hussain B, et al. (2012) Mechanisms of plant defense against insect herbivores. Plant Signaling & Behavior 7(10): 1306-1320.
9. Zaynab M, Fatima M, Abbas S, Sharif Y, Umair M, et al. (2018) Role of secondary metabolites in plant defense against pathogens. Microbial Pathogenesis 124: 198-202.
10. Anand U, Herrera NJ, Altemimi A, Lakhssassi N (2019) A comprehensive review on medicinal plants as antimicrobial therapeutics: potential avenues of biocompatible drug discovery. Metabolites 9(11): 258.
11. Thomford NE, Senthebane DA, Rowe A, Munro D, Seele P, et al. (2018). Natural products for drug discovery in the 21st century innovations for novel drug discovery. International Journal of Molecular Sciences 19(6): 1578.
12. Afonso AF, Pereira OR, Cardoso SM (2020) Health-promoting effects of Thymus phenolic-rich extracts: Antioxidant, anti-inflammatory and antitumoral properties. Antioxidants 9(9): 814.
13. Azab A, Nassar A, Azab AN (2016) Anti-inflammatory activity of natural products. Molecules 21(10): 1321.
14. Recio MC, Andujar IL, Rios J (2012) Anti-inflammatory agents from plants: progress and potential. Current Medicinal Chemistry 19(14): 2088-2103.
15. Martinez FJA, Catalan EB, Lopez MH, Micol V (2021) Antibacterial plant compounds, extracts and essential oils: An updated review on their effects and putative mechanisms of action. Phytomedicine 90:153626.
16. Danish P, Ali Q, Hafeez MM, Malik A (2020) Antifungal and antibacterial activity of aloe vera plant extract. Biological and Clinical Sciences Research Journal.
17. Mahlo SM, Chauke HR, McGaw L, Eloff J (2016) Antioxidant and antifungal activity of selected medicinal

plant extracts against phytopathogenic fungi. African Journal of Traditional, Complementary and Alternative Medicines 13(4): 216-222.

18. Uma K, Huang X, Kumar BA (2017) Antifungal effect of plant extract and essential oil. Chinese Journal of Integrative Medicine 23(3): 233-239.
19. Denaro M, Smeriglio A, Barreca D, Francesco DC, Occhiuto C, et al. (2020) Antiviral activity of plants and their isolated bioactive compounds: An update. Phytotherapy Research 34(4): 742-768.
20. Caesar LK, Cech NB (2019a) Synergy and antagonism in natural product extracts: when 1+ 1 does not equal 2. Natural Product Reports 36(6): 869-888.
21. Rietra RPJJ, Heinen M, Dimkpa CO, Bindraban PS (2017) Effects of nutrient antagonism and synergism on yield and fertilizer use efficiency. Communications in Soil Science and Plant Analysis 48(16): 1895-1920.
22. Franco BE, Martinez MA, Rodriguez MA, Wertheimer AI (2009) The determinants of the antibiotic resistance process. Infection and Drug Resistance 2: 1-11.
23. Kahn LH (2016) One health and the politics of antimicrobial resistance. JHU Press, USA, pp: 200.
24. Ferri M, Ranucci E, Romagnoli P, Giaccone V (2017) Antimicrobial resistance: A global emerging threat to public health systems. Critical Reviews in Food Science and Nutrition 57(13): 2857-2876.
25. Prestinaci F, Pezzotti P, Pantosti A (2015) Antimicrobial resistance: a global multifaceted phenomenon. Pathogens and Global Health 109(7): 309-318.
26. Michael CA, Dominey-Howes D, Labbate M (2014) The antimicrobial resistance crisis: causes, consequences, and management. Frontiers in Public Health, 2: 145.
27. Finkelstein JA, Davis RL, Dowell SF, Metlay JP, Soumerai SB, et al. (2001) Reducing antibiotic use in children: a randomized trial in 12 practices. Pediatrics 108(1): 1-7.
28. Dadgostar P (2019) Antimicrobial resistance: implications and costs. Infection and Drug Resistance 12: 3903-3910.
29. Perron GG, Lee AEG, Wang Y, Huang WE, Barraclough TG (2012) Bacterial recombination promotes the evolution of multi-drug-resistance in functionally diverse populations. Proceedings of the Royal Society B: Biological Sciences 279(1733): 1477-1484.
30. Yim HJ, Hussain M, Liu Y, Wong SN, Fung SK, et al. (2006) Evolution of multi drug resistant hepatitis B virus during sequential therapy. Hepatology 44(3): 703-712.
31. Davies J, Davies D (2010) Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Reviews 74(3): 417-433.
32. Blaser MJ (2014) The microbiome revolution. The Journal of Clinical Investigation 124(10): 4162-4165.
33. Levy SB (2002) Factors impacting on the problem of antibiotic resistance. Journal of Antimicrobial Chemotherapy 49(1): 25-30.
34. Smillie CS, Smith MB, Friedman J, Cordero OX, David LA, et al. (2011) Ecology drives a global network of gene exchange connecting the human microbiome. Nature 480: 241-244.
35. Tiwari R, Rana CS (2015a) Plant secondary metabolites a review. International Journal of Engineering Research and General Science 3(5): 661-670.
36. Guerriero G, Berni R, Munoz-Sanchez J, Apone F, Abdel-Salam EM, et al. (2018) Production of plant secondary metabolites: Examples, tips and suggestions for biotechnologists. Genes 9(6): 309.
37. Wink M (2015) Modes of action of herbal medicines and plant secondary metabolites. Medicines 2(3): 251-286.
38. Kabera JN, Semana E, Mussa AR, He X (2014) Plant secondary metabolites: biosynthesis, classification, function and pharmacological properties. J Pharm Pharmacol 2(7): 377-392.
39. Moore BD, Andrew RL, Külheim C, Foley WJ (2014) Explaining intraspecific diversity in plant secondary metabolites in an ecological context. New Phytologist 201(3): 733-750.
40. Wink M (2010) Introduction biochemistry physiology and ecological functions of secondary metabolites. Annual Plant Reviews Volume 40 Biochemistry of Plant Secondary Metabolism, pp: 1-19.
41. Schmidt TJ, Khalid SA, Romanha AJ, Alves TMA, Biavatti MW, et al. (2012) The potential of secondary metabolites from plants as drugs or leads against protozoan neglected diseases-part II. Curr Med Chem 19(14): 2128-2175.
42. Wink M (2012) Medicinal plants a source of anti parasitic secondary metabolites. Molecules 17(11): 12771-12791.
43. Tiwari R, Rana CS (2015b) Plant secondary metabolites: a review. International Journal of Engineering Research and General Science 3(5): 661-670.

44. Zaynab M, Fatima M, Sharif Y, Zafar MH, Ali H, et al. (2019) Role of primary metabolites in plant defense against pathogens. Microbial Pathogenesis 137: 103728.

45. Pichersky E, Gang DR (2000) Genetics and biochemistry of secondary metabolites in plants: an evolutionary perspective. Trends in Plant Science 5(10): 439-445.

46. Dobetsberger C, Buchbauer G (2011) Actions of essential oils on the central nervous system: An updated review. Flavour and Fragrance Journal 26(5): 300-316.

47. Hernandez I, Alegre L, Breusegem FV, Munne-Bosch S (2009) How relevant are flavonoids as antioxidants in plants. Trends in Plant Science 14(3): 125-132.

48. Pietta PG (2000) Flavonoids as antioxidants. Journal of Natural Products 63(7): 1035-1042.

49. Serafini M, Peluso I, Raguzzini A (2010) Flavonoids as anti-inflammatory agents. Proceedings of the Nutrition Society 69(3): 273-278.

50. Ciumarnean L, Milaciu MV, Runcan O, Stefan CV, Rachisan AL, et al. (2020) The effects of flavonoids in cardiovascular diseases. Molecules 25(18): 4320.

51. Abotaleb M, Samuel SM, Varghese E, Varghese S, Kubatka P, et al. (2018) Flavonoids in cancer and apoptosis. Cancers 11(1): 28.

52. Liskova A, Koklesova L, Samec M, Smejkal K, Samuel SM, et al. (2020). Flavonoids in cancer metastasis. Cancers 12(6): 1498.

53. Costa SL, Silva VDA, Souza CDS, Santos CC, Paris I, et al. (2016) Impact of plant-derived flavonoids on neurodegenerative diseases. Neurotoxicity Research 30(1): 41-52.

54. Mondal A, Gandhi A, Fimognari C, Atanasov AG, Bishayee A (2019) Alkaloids for cancer prevention and therapy: Current progress and future perspectives. European Journal of Pharmacology 858: 172472.

55. Ng YP, Or TCT, Ip NY (2015) Plant alkaloids as drug leads for Alzheimer's disease. Neurochemistry International 89: 260-270.

56. Gutierrez-del-Rio I, Fernandez J, Lombo F (2018) Plant nutraceuticals as antimicrobial agents in food preservation: Terpenoids, polyphenols and thiols. International Journal of Antimicrobial Agents 52(3): 309-315.

57. Vega RJS, Xolalpa NC, Castro AJA, Pérez GC, Pérez RJ, et al. (2018) Terpenes from natural products with potential anti-inflammatory activity. Terpenes and Terpenoids, pp: 59-85.

58. Ateba SB, Mvondo MA, Ngeu ST, Tchoumtchoua J, Awounfack CF, et al. (2018) Natural terpenoids against female breast cancer: a 5-year recent research. Current Medicinal Chemistry 25(27): 3162-3213.

59. El-Baba C, Baassiri A, Kiriako G, Dia B, Fadlallah S, et al. (2021) Terpenoids' anti-cancer effects: focus on autophagy. Apoptosis 26(9-10): 491-511.

60. Sankhuan D, Niramolyanun G, Kangwanrangsan N, Nakano M, Supaibulwatana K (2022) Variation in terpenoids in leaves of Artemisia annua grown under different LED spectra resulting in diverse antimalarial activities against Plasmodium falciparum. BMC Plant Biology 22(1): 128.

61. Shrikanta A, Kumar A, Govindaswamy V (2015) Resveratrol content and antioxidant properties of underutilized fruits. Journal of Food Science and Technology 52(1): 383-390.

62. Moo-Huchin VM, Moo-Huchin MI, Estrada-León RJ, Cuevas-Glory L, Estrada-Mota IA, et al. (2015) Antioxidant compounds, antioxidant activity and phenolic content in peel from three tropical fruits from Yucatan, Mexico. Food Chemistry 166: 17-22.

63. Wojdyło A, Nowicka P, Carbonell BÁA, Hernández F (2016) Phenolic compounds antioxidant and antidiabetic activity of different cultivars of Ficus carica L fruits. Journal of Functional Foods 25: 421-432.

64. Rasouli H, Hosseini-Ghazvini SM-B, Adibi H, Khodarahmi R (2017) Differential α-amylase/α-glucosidase inhibitory activities of plant-derived phenolic compounds: a virtual screening perspective for the treatment of obesity and diabetes. Food & Function 8(5): 1942-1954.

65. Afsar T, Trembley JH, Salomon CE, Razak S, Khan MR, et al. (2016) Growth inhibition and apoptosis in cancer cells induced by polyphenolic compounds of Acacia hydaspica: Involvement of multiple signal transduction pathways. Scientific Reports 6(1): 23077.

66. Lutz M, Fuentes E, Ávila F, Alarcón M, Palomo I (2019) Roles of phenolic compounds in the reduction of risk factors of cardiovascular diseases. Molecules 24(2): 366.

67. Akter R, Rahman H, Behl T, Chowdhury MAR, Manirujjaman M, et al. (2021) Prospective role of polyphenolic compounds in the treatment of neurodegenerative diseases. CNS & Neurological Disorders-Drug Targets 20(5): 430-450.

68. Momtazi-Borojeni AAA, Esmaeili SA, Abdollahi E, Sahebkar A (2017) A review on the pharmacology and toxicology of steviol glycosides extracted from Stevia rebaudiana. Current Pharmaceutical Design 23(11): 1616-1622.

69. Guerrero A, Herranz N, Sun B, Wagner V, Gallage S, et al. (2019) Cardiac glycosides are broad-spectrum senolytics. Nature Metabolism 1(11): 1074-1088.

70. Xiao J, Capanoglu E, Jassbi AR, Miron A (2016) Advance on the flavonoid C-glycosides and health benefits. Critical Reviews in Food Science and Nutrition 56(1): S29-S45.

71. Zhou X, Seto SW, Chang D, Kiat H, Razmovski NV, et al. (2016) Synergistic effects of Chinese herbal medicine a comprehensive review of methodology and current research. Frontiers in Pharmacology 7: 201.

72. Cheesman MJ, Ilanko A, Blonk B, Cock IE (2017) Developing new antimicrobial therapies: are synergistic combinations of plant extracts/compounds with conventional antibiotics the solution?. Pharmacognosy Reviews 11(22): 57-72.

73. Yang Y, Zhang Z, Li S, Ye X, Li X, et al. (2014) Synergy effects of herb extracts: pharmacokinetics and pharmacodynamic basis. Fitoterapia 92: 133-147.

74. Al-Lazikani BA, Banerji U, Workman P (2012) Combinatorial drug therapy for cancer in the post-genomic era. Nature Biotechnology 30(7): 679-692.

75. Sanchez-Vega F, Mina M, Armenia J, Chatila WK, Luna A, et al. (2018) Oncogenic signaling pathways in the cancer genome atlas. Cell 173(2): 321-337.

76. Large TYS, Bijlsma MF, Kazemier G, Laarhoven HWM, Giovannetti E, et al. (2017) Key biological processes driving metastatic spread of pancreatic cancer as identified by multi-omics studies. Seminars in Cancer Biology 44: 153-169.

77. Efferth T, Koch E (2011) Complex interactions between phytochemicals. The multi-target therapeutic concept of phytotherapy. Current Drug Targets 12(1): 122-132.

78. Chen TC, Wang W, Golden EB, Thomas S, Sivakumar W, et al. (2011a) Green tea epigallocatechin gallate enhances therapeutic efficacy of temozolomide in orthotopic mouse glioblastoma models. Cancer Letters 302(2): 100-108.

79. Chen TC, Wang W, Golden EB, Thomas S, Sivakumar W, et al. (2011b) Green tea epigallocatechin gallate enhances therapeutic efficacy of temozolomide in orthotopic mouse glioblastoma models. Cancer Letters, 302(2): 100-108.

80. Malongane F, McGAW LJ, Mudau FN (2017) The synergistic potential of various teas, herbs and therapeutic drugs in health improvement: a review. Journal of the Science of Food and Agriculture 97(14): 4679-4689.

81. Moussaoui F, Alaoui T (2016) Evaluation of antibacterial activity and synergistic effect between antibiotic and the essential oils of some medicinal plants. Asian Pacific Journal of Tropical Biomedicine 6(1): 32-37.

82. Nikkhah M, Hashemi M, Najafi MBH, Farhoosh R (2017) Synergistic effects of some essential oils against fungal spoilage on pear fruit. International Journal of Food Microbiology 257: 285-294.

83. Wei T, Yu Q, Chen H (2019) Responsive and synergistic antibacterial coatings fighting against bacteria in a smart and effective way. Advanced Healthcare Materials 8(3): 1801381.

84. Hayatgheib N, Fournel C, Calvez S, Pouliquen H, Moreau E (2020) In vitro antimicrobial effect of various commercial essential oils and their chemical constituents on Aeromonas salmonicida subsp. salmonicida. Journal of Applied Microbiology 129(1): 137-145.

85. Sakarikou C, Kostoglou D, Simões M, Giaouris E (2020) Exploitation of plant extracts and phytochemicals against resistant Salmonella spp. in biofilms. Food Research International 128: 108806.

86. Yusook K, Weeranantanapan O, Hua Y, Kumkrai P, Chudapongse N (2017) Lupinifolin from Derris reticulata possesses bactericidal activity on Staphylococcus aureus by disrupting bacterial cell membrane. Journal of Natural Medicines 71: 357-366.

87. Bazzaz BSF, Khameneh B, Ostad MRZ, Hosseinzadeh H (2018) In vitro evaluation of antibacterial activity of verbascoside, lemon verbena extract and caffeine in combination with gentamicin against drug-resistant Staphylococcus aureus and Escherichia coli clinical isolates. Avicenna Journal of Phytomedicine 8(3): 246-253.

88. Parvez MAK, Saha K, Rahman J, Munmun RA, Rahman MA, et al. (2019) Antibacterial activities of green tea crude extracts and synergistic effects of epigallocatechingallate (EGCG) with gentamicin against MDR pathogens. Heliyon 5(7): e02126.

89. Surek M, Fachi MM, de Fátima Cobre A, de Oliveira FF, Pontarolo R, et al. (2021) Chemical composition cytotoxicity and antibacterial activity of propolis from

Africanized honeybees and three different Meliponini species. Journal of Ethnopharmacology 269: 113662.

90. Jafri H, Banerjee G, Khan MSA, Ahmad I, Abulreesh HH, et al. (2020) Synergistic interaction of eugenol and antimicrobial drugs in eradication of single and mixed biofilms of Candida albicans and Streptococcus mutans. AMB Express 10: 185.

91. Moussaoui F, Alaoui T (2016) Evaluation of antibacterial activity and synergistic effect between antibiotic and the essential oils of some medicinal plants. Asian Pacific Journal of Tropical Biomedicine 6(1): 32-37.

92. Caesar LK, Cech NB (2019b) Synergy and antagonism in natural product extracts: when 1+ 1 does not equal 2. Natural Product Reports 36(6): 869-888.

93. Hyldgaard M, Mygind T, Meyer RL (2012) Essential oils in food preservation: mode of action, synergies, and interactions with food matrix components. Frontiers in Microbiology 3: 12.

94. Marco-Crook CD, Rakariyatham K, Li Z, Du Z, Zheng J, et al. (2020) Synergistic anticancer effects of curcumin and 3’, 4’-didemethylnobiletin in combination on colon cancer cells. Journal of Food Science 85(4): 1292-1301.

95. Hosseini-Zare MS, Sarhadi M, Zarei M, Thilagavathi R, Selvam C (2021) Synergistic effects of curcumin and its analogs with other bioactive compounds: A comprehensive review. European Journal of Medicinal Chemistry 210: 113072.

96. Manap AAS, Tan WAC, Leong WH, Chia AYY, Vijayabalan S, et al. (2019) Synergistic effects of curcumin and piperine as potent acetylcholine and amyloidogenic inhibitors with significant neuroprotective activity in SH-SY5Y cells via computational molecular modeling and in vitro assay. Frontiers in Aging Neuroscience 11: 206.

97. Ahmadi F, Akbari J, Saeedi M, Seyedabadi M, Ebrahimnejad P, et al. (2023) Efficient synergistic combination effect of curcumin with piperine by polymeric magnetic nanoparticles for breast cancer treatment. Journal of Drug Delivery Science and Technology 104624.

98. Patial V, Mahesh S, Sharma S, Pratap K, Singh D, et al. (2015) Synergistic effect of curcumin and piperine in suppression of DENA-induced hepatocellular carcinoma in rats. Environmental Toxicology and Pharmacology 40(2): 445-452.

99. Jain DP, Pancholi SS, Patel R (2011) Synergistic antioxidant activity of green tea with some herbs. Journal of Advanced Pharmaceutical Technology & Research 2(3): 177-183.

100. Uduwana S, Abeynayake N, Wickramasinghe I (2023) Synergistic antagonistic and additive effects on the resultant antioxidant activity in infusions of green tea with bee honey and Citrus limonum extract as additives. Journal of Agriculture and Food Research 12: 100571.

101. Mohamed SH (2022) Synergistic Effects of Using Essential Oils Blend (garlic, onion and lemon) as a Nanoemulsion on the Productive Performance of Growing Rabbits. Annals of Agricultural Science Moshtohor 60(4): 1063-1076.

102. Jaiswal YS, Williams LL (2017) A glimpse of Ayurveda–The forgotten history and principles of Indian traditional medicine. Journal of Traditional and Complementary Medicine 7(1): 50-53.

103. Mukherjee PK, Banerjee S, Kar A (2018) Exploring synergy in ayurveda and traditional Indian systems of medicine. Synergy 7: 30-33.

104. Cho Y, Kim H, Beuchat LR, Ryu JH (2020) Synergistic activities of gaseous oregano and thyme thymol essential oils against Listeria monocytogenes on surfaces of a laboratory medium and radish sprouts. Food Microbiology 86: 103357.

105. Gavaric N, Mozina SS, Kladar N, Bozin B (2015) Chemical profile, antioxidant and antibacterial activity of thyme and oregano essential oils, thymol and carvacrol and their possible synergism. Journal of Essential Oil Bearing Plants 18(4): 1013-1021.