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# Synergistic effect of actives compounds of medicinal plants on their biologic properties

# Efecto sinérgico de compuestos activos de plantas medicinales sobre sus propiedades biológicas

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**Technological innovation:** vision to the application of synergistic interactions.

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## Resumen

El aumento de enfermedades crónicas no transmisibles y emergentes han generado un incremento en el uso y consumo de plantas medicinales para fines terapéuticos o de prevención. Las plantas medicinales se han utilizado desde la antigüedad en la medicina tradicional o alopática por su impacto positivo sobre la salud humana, debido a que sus compuestos activos tienen diversas actividades biológicas, y sus metabolitos secundarios protegen contra el ataque de los radicales libres y disminuyen el estrés oxidativo. Existen diversos estudios en los que se demuestran los efectos benéficos de una especie vegetal en particular, pero en la medicina tradicional, la combinación de diversas especies vegetales proporciona mejores efectos biológicos debido al efecto sinérgico. Por ello, en este artículo se realizó una revisión de estudios científicos relacionados con la sinergia de la combinación de plantas, que incluyen extractos/extractos, aceites esenciales/aceites esenciales, antioxidantes/fármacos y extractos/pulsos eléctricos. Se realizó una búsqueda completa de literatura utilizando palabras claves en bases de datos (Science Direct, Google Scholar, Scopus, PubMed, Scielo, and Spring Link). Los resultados de las diferentes investigaciones sugieren que la interacción entre los compuestos bioactivos en las plantas aumenta las actividades biológicas como la cardiovascular, antioxidante, antiinflamatoria, antimicrobiana, antiparasitaria, anticancerígena e insecticida. Además, se discuten las consideraciones o limitaciones de los estudios de sinergismo, como la interacción con otras moléculas y los factores que influyen con los efectos sinérgicos y que pueden disminuir sus propiedades biológicas. En conclusión, el sinergismo podría contribuir en diferentes aplicaciones industriales, como en la farmacéutica para el desarrollo de fármacos o en medicina para el diseño de terapias alternativas.

**Palabras clave:** plantas, sinergia, actividad biológica.

## Abstract

The increase in noncommunicable and emerging diseases has generated a rise in the use and consumption of medicinal plants for therapeutic or preventive purposes. Medicinal plants have been used in traditional medicine for their positive impact on human health, due to their active compounds having various biologics activities, and their secondary metabolites protect against free radical attacks and decrease oxidative stress. There are several studies showing the beneficial effects of a particular plant species, but in traditional medicine, the combination of various plant species provides better biological effects due to the synergistic effect. Therefore, in this article, a review of scientific studies related to the synergy of the combination of plants was carried out, including extracts/extracts, essential oils/essential oil, antioxidants/drugs, among others. A comprehensive literature search was conducted with keywords in databases (Science Direct, Google Scholar, Scopus, PubMed, Scielo, and Spring Link). The results of different investigations suggest that the interaction between bioactive compounds in plants increases biological activities such as cardiovascular, antioxidant, anti-inflammatory, antimicrobial, anticancer, among others. In addition, it discusses the considerations or limitations of synergistic studies, such as interaction with other molecules and factors that influence synergistic effects and may decrease their biological properties. In conclusion, synergy could contribute to different industrial applications, as in the pharmaceutical for the development of drugs or in medicine for the design of alternative therapies.

**Keywords:** plants, synergy, biological activity.

## 1. Introduction

According to World Health Organization date, 71% of all deaths worldwide are due to chronic non-communicable diseases (NCDs); 77% of these percentage are in low-and middle-income countries, the NCDs including heart disease, diabetes, obesity, chronic lung disease and cancer (WHO, 2021). Recently, has grown dramatically used of traditional medicinal in developing countries due to increment of NCDs (Gauthier et al., Went et al., 2020). In 2018, approximately 80% a global population utilized nature products for diseases prevention and care-health (Acosta-Recalde et al., 2018). Nigeria, Bangladesh, and India use *Momordica charantia* L. to lower blood sugar levels (Seetaloo et al., 2019). Apart from traditional medicine, exercise, dietary and lifestyle modification are necessary for the prevention of NCDs. Another reason for this consumption is emerging diseases such as the occasioned by COVID-19, which has been generated a pandemic. A performed a quantitative, correlational, nonexperimental study on the use and consume of herbal medicine in Ecuador during this pandemic (De los Ángeles et al., 2020). Of the 829 participants, 52.2% consumed in greater quantities eucalyptus and 23.6% ginger.

Traditional medicine (TM) has been used in all cultures for the treatment of diseases or health maintenance (Mazumder & Rhaman, 2008; Reyes-Munguía et al., 2016). It is characterized by the use of a single formula with mixtures of different plants, called medicinal plants (Wang et al., 2012; Caesar & Cech, 2019). Medicinal plants represent a critical factor for development of drugs or alternative therapies (Shan et al., 2021). In China has been identified 2700 medicinal plants usually used in herbal medicine (Shan et al., 2021). In Mexico, the Ministry of Environment and Natural Resources esteem 4000 medicinal plants, of which only 3000 have been registered (Secretaría de Medio Ambiente y Recursos Naturales, 2021). Medicinal plants must have active ingredients or secondary metabolites that possess curative or preventive biological activities for some disease; can be a whole plant or plant parts (Santillán, 2012; Abubakar & Haque, 2020). Secondary metabolites, such as polyphenols, terpenes, steroids, glycosides, and alkaloids are extracted from inert material using different extraction processes (decoction, infusion, percolation, maceration, ultrasound-assisted extraction, Soxhlet extraction, and microware-assisted) (Hęś et al., 2019; Belščak-Cvitanović et al., 2018). Of these metabolites polyphenols are antioxidants that (i) inhibits oxidation totally or partially, (ii) eliminate free radicals, (iii) convert free radicals into less harmful molecules, (iv) decrease oxidative stress (Liu, 2020; Nanda & Madan, 2021). Free radicals have a single electron in their last orbital; this unpaired electron extracts an electron from other molecules and induces its oxidation (Hernández-Espinoza et al., 2019; Wang et al., 2021). Of all free radicals, ROS are higher dangerous due to increase oxidative stress (Razavi & Hosseinzadeh, 2020). If free radicals increase oxidative stress occurs in the cell and cellular compounds, such as DNA, lipids, and membrane proteins, would be injured (Carvajal, 2019; Wen et al., 2020).

Medicinal plants and nature foods provide superior protective effects against oxidative stress due to the synergistic interrelations between the different antioxidants within them (Fleming & Luo, 2021; Wang & Zhu, 2017). As a result of several studies, the use of plants has increased in recent years, suggesting its use as alternative medicine. They have properties, mainly antioxidant, antimutagenic, anticancerogenic, and antimicrobial (Alonso-Castro et al., 2017; Reyes-Munguía et al., 2016; Wang et al., 2018). However, these studies are usually to individual plants, whether evaluation their extracts or essential oils. The mixture of plants provides better biological effects due to the synergy between bioactive compounds, mainly antioxidants (Hęś et al., 2019; Pereira et al., 2015; Venkatadri et al., 2020). To try to use the advantages of this type of interaction, Pereira et al. (2015) mentions that there are studies based on the biochemistry of plants, intending to explain and understand the reaction mechanisms of the combination of different plants. Initial field examinations of synergy application between plant-derived compounds were carried out on antimicrobial activity through BMI (minimum inhibitory concentration) and fractional inhibitory index (FIC) (Dimitrijevic-Brankovic et al., 2007; Lachowicz et al., 1998). In addition, plant-derived compounds were evaluated along with antibiotics, lactic acid, NaCl, fatty acids esters, and potassium sorbate had present results from favourable interactions against pathogens bacteria (Dimitrijevic-Brankovic et al., 2007; Lachowicz et al., 1998; Santiesteban-López et al., 2007; Yamazaki et al., 2004). In this context, this study aimed to bring to the scientific community a review on different research conducted of the synergy application and the considerations that must have these studies.

## 2. Methodology

### 2.1 Search strategy and selection criteria

The present review article considered the literature published on synergy. All the available information on synergy studies was collected from electronic databases: Science Direct, Google Scholar, Scopus, PubMed, Scielo, and Spring Link. There was no limitation applied to the language. The search terms used were ("synergism" [All Fields]), ("synergistic effect" [All Field]), ("medicinal plants" [All Field]), ("oxidative stress" [All Field]), ("synergy plants" [MeSH Terms]), ("synergy antioxidant" [MeSH Terms]), ("antioxidants" [MeSH Terms]), ("synergy essential oils" [All Fields]), ("bioactive compounds" [All Fields]), ("synergy factors" [MeSH Terms]), ("synergy bioactive compounds" [All Fields]). Articles of Open access were included in this article.

According to the search terms used, the authors examined relevant studies and sequentially screened their titles and abstracts for eligibility. Research articles, reviews, and observational studies from 2012 to 2021 that contained the keywords in the title, abstract, and subject description were eligible for the review. The full texts of potentially eligible studies were retrieved and excluded in case of insufficient date, irrelevant research question, and inappropriate research design.

Analytical techniques applied to measure synergy, including (i) spectrophotometric assays: 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2-azinobis (3-ethyl-benzothiazoline-6-sulphonic acid (ABTS), ferric reducing ability of plasma (FRAP), total antioxidant capacity (TAC), (ii) biological systems: living cell (HepG2 cells and carcinoma HT-29 cells), (iii) animals, (iv) *in silico* assays, and (v) tissue cultured. Additionally, evaluates the polyphenol total content (flavonoids, tannins, phenols, etc.) and different biological activities.

### 2.2 Study selection

A total of 100 studies were obtained during the literature search. After analysis using our inclusion and exclusion criteria, were 76 excluded, and 24 included in the present work.

### 2. 3 Data analysis and representation

The selected studies were integrated in Table 1, according to the following criterions: plant or substance used, part used, type of extract, proportion, biological activity, test evaluated, result, identified bioactive compounds, and reference.

**Table 1.** Synergistic effects of different plants and compounds on several biological activities.

| Plant or substance used | Part used | Type of extract | Proportion of mixture | Biological activity | Test | Result | Identified bioactive compounds | Reference |
|---|---|---|---|---|---|---|---|---|
| *Radix genre: Salviae multiorrhizae (RSM) Ophiopogonis Japonici (ROJ) Astragali Mongolici (RAM) Puerariae lobatae (RPL)* | 3D structures | NM | NM | Cardiovascular | A novel system biology model integrating: Oral bioavailability, drug-likeness screening, and target identification | RSM shown synergy with each of the other three plants. | 118 bioactive compounds | Wang et al., 2012 |
| *Hibiscus sabdariffa* L<br>+<br>*Olea europea* L | F<br><br>L | E<br><br>A | 13:2 v/v | Cardioprotector<br>Vascular activity | Determination of antioxidant and cytoprotective effects in cultured HUVECs | Extract combined showed high cardiac and vascular protective activities that each single extract. | Hibiscus acid<br>Oleuropein isomer<br>Two glucoside isomers of luteolin | Micucci et al., 2015 |
| CFO: Sheng-ma (*Cimicifuga foetida* L)<br>+<br>AME: Huang-qi (*Astragalus membranaceus* var. *mongholicus* (Bunge)) | R | E | 1:1 v/v | Antioxidant | Determination of antioxidant activity:<br>DPPH<br>FRAP<br>ABTS<br>Determination of protective effect against $H_2O_2$-induced oxidative damage in HepG2 cells | The combination of calycosin and isoferulic acid resulted in a synergy in DPPH (1.062 mg/mL), FRAP (8.706 mmol/g), and HepG2 cell bioassay (CI, 0.442). | Calycosin<br>Formononetin<br>Ferulic acid<br>Isoferulic acid | Wang et al., 2014 |
| Egyptian *Chlorella vulgaris* (GVE)<br>+<br>Malaysian *Ganoderma lucidum* (GLE) | M<br><br>MU (MY + FB) | E<br><br>A | 63.5 µg/mL of CVE + 4.1 µg/mL GLE | Antioxidant<br>Anti-inflammatory | Total phenolics<br>Total flavonoids<br>Total triterpenoids<br>Total tannin<br>Determination of antioxidant:<br>TAC<br>DPPH<br>Anti-inflammatory activity | The mixture of extracts was significantly better than the control, anti-inflammatory drug (Dex). GLE-CVE decreased in 13.6 µg/mL the anormal elevation in the proliferation of LPS-exposed and Dex 30.4 µg/mL. | 2,5-dihydroxy benzoic acids<br>Gallic acid<br>RU | Abu-Serie et al., 2018 |
| Grapefruit (*Citrus paradisi*) (GFJ)<br>+<br>Aripiprazole (ARI) | P | J | 2 mg/Kg ARI and 0.5 mL GFJ along with $H_2O_2$ | Antioxidant<br>Anti-inflammatory | Animals: $H_2O_2$ induced oxidative stress in mice | ARI + GFJ decreased pro-inflammatory cytokines (IL-2, IL-10 and TNF-α) and biochemical | Naringin | Zargar et al., 2018 |

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| | | | | | | markers (ALT, 38.99 U/mL) | | |
| *Salvia officinalis* L. (SAE) + Loperamide (LOP) | L | A | 50 mg/Kg SAE + 5 mg/Kg LOP + castor oil (CO-induced diarrhea) 5 mL/Kg | Antidiarrheal | Determination of antioxidant Antidiarrheal activity | SAE and Mix against Co-induced diarrhea | ND | Jedidi et al., 2019 |
| *Bunium persicum* and *Rosmarinus officinalis* + Citric acid | S | EO | NM | Antioxidant | DPPH<br>Cupric ion-reducing power | The combination can be applied to increase the oxidative stability of virgin olive oil. | γ-terpinene<br>ρ-cymene<br>cuminaldehyde<br>α-pinene<br>Camphene<br>Limonene<br>Camphor<br>Verbenone | Keramat et al., 2016 |
| Carotenoids of Carrot (CE) and Marigold (ME) + Azelaic acid (AA) | NM | NF with HG into NLC | NM | Antioxidant<br>Antibacterial<br>Anti-inflammatory | Antioxidant activity<br>*In vitro* determination of antimicrobial activity | HG-NLC-ME/CE-AA showed antioxidant and antibacterial activities. Decreased the secretion of IL-1β and TNF-α proinflammatory cytokines | ND | Lacatusu et al., 2020 |
| Binary combination:<br>Black pepper<br>Cumin<br>Bay leaf<br>Garlic<br>Coriander<br>Ginger<br>Onion<br>Turmeric<br>Mustard | S<br>S<br>L<br>BU<br>S<br>R<br>BU<br>R<br>S | EO | 1:1 v/v | Antibacterial<br>Antioxidant | Antibacterial activity:<br>*Salmonella typhimurium*<br>*Bacillus cereus*<br>*Listeria monocytogenes*<br>*Micrococcus luteus*<br>*Staphylococcus aureus*<br>*Escherichia coli*<br>Antioxidant activity:<br>DPPH | The combination of coriander/cumin seed oil exhibited antioxidant (CI=0.79) and antibacterial effects. | Coriander: linalool<br>Cumin: ρ-coumaric acid | Bad & Chattopadhyay, 2015 |
| *Cucumis myriocarpus*<br>*Ekebergia capensis*<br>*Bolusanthus speciosus*<br>*Solanum panduriforme*<br>*Prunus africana*<br>*Searsia lancea*<br>*Protea caffra* | S, L<br>L<br>BA<br>FR, ST<br>L<br>L<br>BA, F, L, S | E, A, M, DCM, PE | Different combinations Example: 2.5/0.125, 0.625/2.5, 0.156/0.156 mg/mL | Antibacterial | Antibacterial synergy studies:<br>Anti-gonococcal<br>Checkerboard titration bioassay<br>Time-kill bioassay | Extracts can be used individually or in combination with antibiotics due to showed potentially antibacterial effect. | ND | Vambe et al., 2018 |
| *Callistemon lanceolatus and Ocimum gratissimum* | NM | EO | 1:1 v/v | Antibacterial<br>Antioxidant | Antioxidant activity:<br>DPPH | The results of binary mixtures of essential oils | 1,8-cineole<br>α-pinene<br>dl-limonene<br>isoeugenol | Sharma et al., 2020 |

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| + *Citronella java, Cymbopogon flexuosus, Mentha longifolia, and Vitex negundo* | | | | | Antibacterial activity: Dilution method | and the other components provide antimicrobial and antioxidant effect tests | eugenol germacreme-D caryophyllene oxide citronellal elemol rosifoliol cardinene cis-carane terpinolene cis-myrtanol cubebol α-elemene | |
| Black pepper Cinnamon Clove | FR BA B | EO | 2.52% black pepper, 2.14% cinnamon 2.83% clove | Antibacterial Antifungal Antioxidant | Determination of minimum inhibitory concentration | Antibacterial activity against *Pseudomonas aeruginosa Listeria monocytogenes Salmonella typhimurium* | Clove: Eugenol, β-caryophyllene, eugenyl acetate, and caryophyllene oxide Cinnamon: cinnamaldehyde, cinnamyl acetate, and -β-caryophyllene. | Purkait et al., 2020 |
| 1,8-cineole + Camphor 39 compounds | - | - | 1:1 w/w | Insecticide | Cuticular penetration analyses | High penetration in larvae of *Trichoplusia ni*. | | Tak & Isman, 2017 |
| *Artemisia iwayomogi* + *Curcuma longa* | L R | E | 1:1 v/v | Antihyperlipidemic | Antioxidant activity Tissue cultured: Histopathological analysis | The was combined extract more effective on a high-fat diet model compared to its separate administered. | ND | Han et al., 2015 |
| *Curcuma longa* (CL) + *Nigella sativa* (NG) | R S | E | 1:1 v/v | Protector against Adriamycin | Animals and tissue cultured: Biochemical assessment Histopathological examination | Ethanolic extrdeteract of CL and NS resulted in protector effect on damaged renal tissue. | Curcumin Thymoquinone | Mohebbati et al., 2017 |
| *Curcuma longa* (AgNPs) + *Zingiber officinale* (AgNPs) | R | A | 1:5 v/v 20 mL of 1M AgNO3 and 80 mL of extract | Anticancer | *In vitro* anticancer activity | AgNPs synthesized show potential anticancer activity in human colon carcinoma cells (HT-29). | ND | Venkatadri et al., 2020 |
| Sumac *(Rhus hirta)* + Raspberry *(Rubus strigosus)* | FR | M | 1:1 v/v | Anticancer Antioxidant | Antioxidant capacity Cytotoxic activity | The mixture was the most inhibitory cell proliferation that sumac and raspberry individuals. | ND | Wang et al., 2014 |
| *Laurus nobilis* (LNEO) + | L | EO | Binary mixtures: 1:1, 1:2, and 2:1 | Anticholinesterasa Antioxidant | Anticholinesterase activity DPPH ABTS | LNEO interacts synergistically very strongly with | LNEO: 1,8-cineole, linalool, camphene, sabinene, | Yakoubi et al., 2021 |

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| *Lavandula stoechas* (LSEO) and *Mentha pulegium* (MPEO) | | | Ternary mixtures: 1:1:1, 2:1:1, 1:2:1, and 1:1:2 | | | LSEO or MPEO in a ratio of 2:1. | methyl eugenol, eugenol, and α-pinene | |
| Fourteen medicinal plants Genres: *Artemisia, Hyssopus, Lavandula, Lippia, Mentha, Tanacetum, and Thymus* | L | EO | Binary combination 1:1 w/w | Anti-trypanosomal | Determination of anti-trypanosomal activity | *Mentha rotundifolia, Hyssopus officinalis, Thymus vulgaris, Thymus zygis* showed antitrypanosomal activity | Piperitenone oxide, terpinene-4-ol 1,8-cineole, β-pinene, pinocanfone, sabinene, α-pinene, carvacrol Thymol, p-cymene, γ-terpinene, linalool | Guardo et al., 2017 |
| Curcumin Flavone Resveratrol + Drugs: Anthelmintic (flubendazole and praziquantel) Anticancer (imatinib and vandetanib) | - | - | 1:1 | Antischistosomal activity | Antischistomal activity based on a host-parasite *Bioamphalaria glabrata* | Antioxidants exhibit an antischistosomal effect. Also, many antioxidants improved the action of anthelmintic drugs. | ND | Gouveia et al., 2019 |
| β-caryophyllene, cinnamaldehyde, and eugenol of cinnamon + β-caryophyllene, cinnamaldehyde and eugenol of clove | - | Components commercially obtained | 1:1 | Anti-biofilm | Determination of biofilm eradication activity against preformed biofilms | Inhibition formation of biofilm of *Listeria monocytogenes* and *Salmonella typhimurium* | | Purkait et al., 2020 |
| *Syzygium aromaticum Cymbopogon citratus Aeollanthus heliotropioide* | F L AP | EO EO | NM | Antifungal Anti-biofilm | Determination of antifungal activity *In vitro* anti-biofilm activity assay | The combinations of essential oils exhibited an anti-biofilm and antifungal activity against *Candida spp*. | Linalool β-famesene α-caryophyllene Terpineol Germacrene Eugenol Geranial Citronellol γ-dodecalactone | Ngo-Mback et al., 2020 |
| Fennel: *Foeniculum vulgare* Mill + Calcium sennosides (senna leaves) | S | Commercially obtained | 250 μg/mL of sennosides and 200 μg/mL of fennel | Antioxidant Anti-inflammator Anti-mutagenic | Living cell (human lymphocyte cultures) | Treatment against oxidative and inflammation effects of ionizing radiation. | ND | Farid et al., 2020 |
| *Piper nigrum* + Electrical pulses | F | E | - | Provide cell death of breast cancer | Total phenolic contents Cytotoxic activity | The application of electrical pulses aids achieving | Caryophyllene Piperine Piperidine Isobutylhexadeca | Poompavai & Gowri, 2021 |

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| | | | | | | antioxidant and phenolic-rich extracts | 2,4-dienamide<br>Piperlonggumi nine<br>Ianceol<br>Curlone | |
| F: Flower, L: leaves, S: Seed, R: Rhizome, FR: Fruit, BA: Bark, B: Bud, BU: Bulb, M: Microalga, MU: Mushroom, MY: Mycelium, FB: Fruit body, SB: Stem bark, ST: Stem, AP: Aerial parts, E: Ethanol, A: Aqueous, M: Methanol, DCM: Dichloromethane, PE: Petroleum ether, EO: Essential oil, NF: Nanostructured formulations, HG: Hydrogel, NLC: Nanostructured lipid carriers, NM: No mention, ND: No determined, AgNPs: silver nanoparticles. | | | | | | | | |

## 3. Results and discussion

Studies of medicinal plants used together showed a synergistic effect in cardiovascular, antioxidants, antibacterial, antihyperlipidemic, insecticide, anticancer, anticholinesterase, anti-biofilm activities, among others (Table 1). Leaves, seeds, rhizomes, fruits, flowers, bark, bud, stem bark, and were plant parts used for extracts preparation. No in all studies the phytochemicals were identified, but these could be responsible for the observed activities.

Cardiovascular studies show that the effect of the combination provide better effects that individual extracts. Synergy has even been evaluated within *in silico* assays; this strategy permits better molecules election before testing *in vivo* or *in vitro* tests (Dana et al., 2019). Wang et al. (2012) mention that the synergic effect between bioactive compounds of RSM and other three plants could act on same targets (Table 1). For example, 39 compounds of RSM and 9 of RPL can be modulated prostaglandin G/H synthase 2. A total of 118 compounds 40 in RSM, 44 in RAM, 12 in RPL, and 14 in ROJ were utilized to synergies interactions. Hibiscus acid is a compound with cardiovascular activity.

Antioxidants potentiate the effects of drugs (Table 1), such as ARI that increase its oral bioavailability due to that GFJ inhibited CYP3A4 and CYP2D6 iso-enzymes that participate on the elimination of ARI (Zargar et al., 2018). Other authors have also considered synergies possible between other molecules. Palmitoylethanolamide (PEA) and natural antioxidants, for example, flavonoids (polydatin, luteolin anthocyanins, among others) that could enhance its pharmacology effects, firstly the anti-inflammatory (Peritore et al., 2019). The regulating pathways that modulate the anti-inflammatory effect have also been studied in synergies. Lee et al., (2020) analyzed ethanolic extracts *Allium hookeri* (*A. hookeri*) and *Curcuma longa* (*C. longa*) mediated animal study, immunohistochemical, immunofluorescence analyses and western blotting. They concluded that *A. hookeri* and *C. longa* co-treatment (3:7) modulate the COX-2 and NF-kB pathways. This modulation suppressed these pathways that controls various stages of inflammation (pro-inflammatory cytokines and TNF-α).

Also, curcumin has been reported to reduces renal injury; caused for drugs such as Adriamycin. Other compounds, such as thymoquinone functions protective agent on nephrotic syndrome (Mohebbati et al., 2017).

Bioactive compounds and antidiarrheal drugs can be present synergy for their action mechanisms. For example, antidiarrheal drugs have a specific mechanism action, but bioactive compounds have different mechanisms. By combining them modulate different biochemical pathways and act on different targets in the intestine (Jedidi et al., 2019).

Food industries could be beneficiated for the synergy between compounds bioactive of plants and synthetic antioxidants. This synergy could be decreased lipid oxidation; factor that produce deterioration of oils and fat containing products (Keramat et al., 2016). Moreover, the growth of biofilms in food industry increases the opportunity of contamination of products. Finding compounds that present anti-biofilm activity could help this problem. Purkait et al., (2020) reported that the cinnamaldehyde/eugenol combination is against preformed biofilm in *Listeria monocytogenes* (Table 1). In the study of Ngo-Mback et al. (2020) anti-biofilm activity against *Candida spp* could be attributed to size and chemical composition of compounds. These characteristics should damage organic structure and biofilm. Antifungal activity is generated by the interference in ergosterol biosynthesis, the major component in the membrane of fungi. This information could be utilized to design antioxidant, antibacterial, and antifungal natural products.

The conventional anticancer treatments (chemotherapy and radiation) kill cancer cell but damaging normal cell at the same time (Wang et al., 2014). Utilizing combination mixtures of extracts or bioactive compounds could contribute to the design of alternative therapies with effective results at an affordable cost and decreasing the drug´s dosage. For example, the combination of curcumin with other compounds decreases proliferative factors related to different types of cancer (Hosseini-Zare et al., 2020).

Antibacterial and antiparasitic activity is another investigation line of synergistic interactions with interesting results for the clinical area in the development of drugs (Table 1). For example, in the study of Gouveia et al. (2019) reported that the synergistic effect between antioxidants and drugs can be associated with diverse targets in Schistosomiasis or mechanisms of action. The combination blocked or inhibited parasite development. This information could be used to development of drugs for prophylaxis and applied in regions with high levels of reinfection. In the case of multidrug-resistant bacterial strains are serious problem that generates development of new antibiotics and investigation of compounds with antibacterial activity. Antibacterial synergy is based on the principle of increasing efficacy, reducing toxicity, decreasing adverse effects, increasing bioavailability, decreasing doses, and reducing advances in antimicrobial resistance (van Vuuren & Viljoen, 2011).

These studies suggest that combination mixtures show synergy with better biological activities than the use of individual extracts or compounds. However, further detailed studies should be conducted to determine the specific mechanism of action.

### 3.1 Considerations of synergy studies

Phytochemicals could be present low biological effects due to several factors, such as mixture inappropriate or if the participant compounds bond with the hydrogen of the hydroxyl groups, decreasing their ability to capture free radicals decreases (Phan et al., 2018). The content of secondary metabolites depends on the type of plants used and their growing conditions (soil type, nutrients, clime, geography localization, among others). For example, the increasing temperature might cause stress in the plants and alter the production of bioactive compounds (Cahyaningsih et al., 2021). Solvent types are an important factor due to their physical properties, as polarity influences the affinity of metabolites during extraction process. Polar and semi-polar metabolites secondary of plants can be extracted using polar solvents (water, ethanol, and methanol) and nonpolar metabolites are extracted using nonpolar solvents (Abubakar & Haque, 2020; Seetaloo et al., 2019). The proportion of mixture and administered doses influences on synergy assays, Guardo et al. (2017) indicated the existence of synergistic and antagonistic effect depends in the concentration level administered on anti-trypanosomal activity.

Also, antioxidants interact even with macromolecules, such as blood proteins, digestive enzymes, or intestinal transport, including with food matrices (Claudie et al., 2013; Gonzales et al., 2015). These interactions might increase or decreased its biological activities and bioavailability (Wang et al., 2014; Yang et al., 2011). For example, food matrices can cause variation in the bioavailability of anthocyanins by affecting their absorption and antioxidant capacity. Their properties will influence a possible competition for their absorption or cellular transport; therefore, it is essential to isolate the polyphenols of other soluble compounds before use to increase synergistic interactions safely (Claudie et al., 2013; Gonzales et al., 2015; Herranz-López et al., 2012; Yang et al., 2011).

Furthermore, other factors influence in the interrelations of bioactive molecules of plants or combination with other compounds. Toxicity must be evaluated, the main methods to evaluate the safety of bioactive substances are toxicological studies, such as immunotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity, among others (Espinoza et al., 2017). Despite the interest in the effects of the combination of mixture of plants, there is still the absence of protocols related to which model of reference is appropriate to study the effects of the combination, this makes it difficult to the studies, and quality and safety standards should also be stablished (Caesar & Cech, 2019).

## 4.Conclusion

The synergy between bioactive compounds present in plants is the line of research open to future studies with favourable contributions to health well-being. Synergy presents potential importance across many disciplines, like pharmaceutical, nutraceutical, environmental, agriculture, and food industry. For example, in the pharmaceutical development of antibacterial, antiparasitic, and antifungal drugs. In the nutraceutical to design new alternative therapies. In the environment and agriculture to develop natural insecticides for crop protection. The food industry can apply substances against pathogens of food products and antioxidants to protect against lipidic oxidation.

Additionally, it is necessary to investigate the mechanisms of action of synergy, these provide information on its effects on the body, to identify appropriate doses and safety of bioactive compounds combination. Finally, it is critical to collect all possible elements that may impede or influence synergistic interactions to obtain the best possible effects of bioactive compounds synergy.

## Conflict of interest statement

The authors declare that there is no conflict of interest.

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