

Advances in Clinical and Medical Research

Genesis-ACMR-4(4)-63
Volume 4 | Issue 4
Open Access
ISSN: 2583-2778

Synergistic Interactions between Bioactive Substances

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Citation: Estevam Barbosa PA, Castilho Lopes CC, Scremin M, Rosa IT, dos Santos PS, et al. (2023) Synergistic interactions between bioactive substances. *Adv Clin Med Res.* 4(4):1-8.

Received: August 30, 2023 | **Published:** September 11, 2023

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Abstract

Introduction: Sympathy for synergistic actions between bioactive substances has increased in recent years due to recent paradigm shifts. The search for selective molecules with a single mechanism of action, the behavior most frequently sought in research on new drug candidates, has been giving way to the development of multiple therapies, with the aim of acting simultaneously and concomitantly on various therapeutic targets.

Objective: Review the literature to verify synergistic interactions between bioactive substances and their importance.

Methods: This study constitutes a systematic review, classified as exploratory and descriptive. The elaboration of the research was bibliographical research in electronic databases on methods associated with RSL (Systematic Literature Review) and SMARTER applications (Simple Multi-Attribute Rating Technique using Exploiting Rankings).

Results: A comprehensive systematic literature search yielded a total of 772 articles referring to synergy between bioactive substances. Of these, 36 articles became eligible to compose this systematic review.

Conclusion: The study concluded that most efforts devoted to natural product knowledge are typically devoted to reducing complexity and identifying unique active components for drug development.

Keywords

Synergistic Interactions; Bioactive Substances; Synergy

Introduction

The term synergy comes from the Greek word “synergos” which means working together [1-2], and as well perceived and quoted by Buckminster Fuller (1968), the “universe is synergistic, life is synergistic” [3]. Synergy is broadly defined as the interaction or cooperation of two or more substances, organizations or other elements to produce a combined effect greater than the sum of its separate parts [4-5]. In anatomy, it is the combined action of muscle groups that results in a force greater than that which can be generated by individual muscles [6-7]. While in pharmacology synergism is described as an approach used for the treatment of multidrug resistant bacterial infections, cancerous and multifactorial diseases in which the use of pharmacological and therapeutic agents can affect several pathways making the treatment more effective [4-8]. In addition, Mosby's Dictionary of Complementary and Alternative Medicine define synergism or pharmacological synergy as the effect of combined components that when interacting with each other produce new and improved effects [4].

On the other hand, additive interactions are those in which the effect of mixing two or more substances is equal to the simple sum of the effects, isolated [8-10]. Sympathy for synergistic actions between bioactive substances has increased in recent years due to recent paradigm shifts. The search for selective molecules with a single mechanism of action, the behavior most frequently sought in the research of new drug candidates, has been giving way to the development of multiple therapies, with the aim of acting

simultaneously and concomitantly on various therapeutic targets [11].

In this way, the concepts cited above clearly show that when substances interact synergistically or potentially the effects of their combinations together are greater than what could be expected based on the individual contribution of each of their components, and is greater than the effect expected additive [4-12]. In this context, the objective of this study was to review the literature to verify the synergistic interactions between bioactive substances and their importance.

Methods

This study constitutes a systematic review, classified as exploratory and descriptive. The elaboration of the research was bibliographical research in electronic databases on methods associated with RSL (Systematic Literature Review) and SMARTER applications (Simple Multi-Attribute Rating Technique using Exploiting Rankings). The work carried out is qualitative and quantitative. Qualitative data analysis was performed intuitively and inductively during the survey of the theoretical framework. It is also quantitative using the multicriteria method. In addition, there is also a numerical experimental study in order to simulate an article selection situation based on the observed criteria.

Based on bibliographical research, located in the following databases: US National Library of Medicine Scientific Electronic Library on-line (SCIELO), Latin American Caribbean Health Sciences Information System (LILACS), Science Direct (Elsevier) and Embase. Complementarily, searches were carried out based on bibliographical references of studies that relevantly addressed the topic on the Google Scholar search platform. The search in the databases was carried out using the terminologies registered in the Health Sciences Descriptors created by the Virtual Health Library developed from the Medical Subject Headings of the US National Library of Medicine, which allows the use of common terminology in Portuguese, English and Spanish. The present study sought to investigate the literature on synergistic interactions between bioactive substances and their importance. For this purpose, the descriptors “synergistic interactions and bioactive substances” were used, initially in English, and in a complementary way in Spanish and Portuguese. For a better update, the word “synergy” was added to the search.

As a tool to support the decision in the selection and prioritization of articles, a set of criteria were considered essential to represent the state of the art of the subject object of the research. This method has the following characteristics: (i) rigorous logic allows acceptance of the method as a decision support tool; (ii) simple to understand and apply with easily interpreted results. References from selected papers were also searched for other documents of potential interest. Once qualified for full-text evaluation, articles were included in the qualitative review if they met the following inclusion criteria: a) they contained data on synergistic interactions; b) bioactive substances. Articles were excluded if they were reports, banners or conference abstracts. There was no review of confidential health information and the study was non-interventional. Therefore, ethics committee approval was not required. To the end, the result obtained totaled 36 articles that contemplated the desired characteristics for the study.

Results

A comprehensive systematic search of the literature yielded a total of 772 articles referring to the synergy

between bioactive substances. From there, we chose the SMARTER method (Simple Multi-Attribute Rating Technique using Exploiting Rankings). Of these studies, 64 articles were suitable for full-text screening and 36 articles were included for data extraction. Of these, 2 studies were excluded due to overlapping data. Here, 36 articles were included for systematic review. In (Figure 1), we describe the strategy for selecting articles on the topic in question.

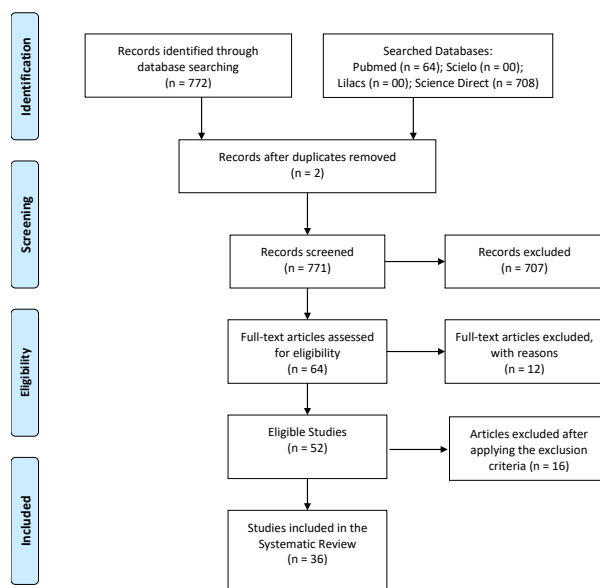


Figure 1: Article Search Strategy

Discussion

Pharmacodynamic Synergism

Pharmacodynamic synergy can occur through complementary actions, in which substances interact with various points in a given pathway resulting in the up regulation of a process that affects the target of the active agents, or in the down regulation of recurrent mechanisms [13]. In addition to this, it involves a process where the synergistic compound binds to an anti-target (molecule or substance that prevents the action of active agents) effectively inhibiting the disease target from neutralizing the therapeutic effect of the active component [14].

As an example, we have *Ginkgo biloba* L. (Ginkgoaceae) which in several studies has shown to have a synergistic neuro protective effect in vitro and in vivo, inhibiting the formation of free radicals and ROS, regulating the gene expression of mitochondrial targets and reducing the excessive stimulation of cells nerves by neurotransmitters [15,16]. In addition to this, another important occurrence of pharmacodynamic synergism by components of a plant species was attested between the constituents of artemisinin, applied in the treatment of chloroquine-resistant malaria. Interestingly, the concentration of artemisinin in the aqueous extract is low when compared to clinical doses. Despite this, the extracts were more efficient than the isolated substance [17]. This fact occurs due to the synergistic behavior between

its methoxylated flavonoids that optimize the action of artemisinin, increasing the speed of the reaction, leading to the release of reactive oxygen species (ROS) for the destruction of the parasite, and even inhibiting resistance mechanisms [18].

Pharmacokinetic Synergism

Plants contain compounds that do not have specific pharmacological effects, but increase the solubility, absorption, distribution or metabolism of their active constituents, which will result in greater bioavailability, allowing for greater efficacy of the extract compared to the individual constituents [19]. Studies have shown that hypericin, when combined with substances (isorquercitrin, miquelianin, naphthodianthrone hypericin, procyanidin B2 and flavonoid hyperosides), from different biochemical classes, significantly increases the solubility and oral bioavailability of hypericin [20]. Researchers analyzed the function of carbohydrates, amino acids, choline, and highly abundant organic acids in plant cells. It was verified that these molecules probably play a role in the production of “natural eutectic solvents”, which function as a third liquid phase, with intermediate polarity between lipids and water, favoring the solubilization of the mixture of plant substances [21].

Absorption can be enhanced through a variety of mechanisms that include efflux pump inhibition, permeability optimization, inhibition of enzymes that convert bioactive agents into excretable or inactive forms, and induction of enzymes that convert prodrugs. In active drugs [22]. The presence of compounds that improve the solubility and bioavailability of bioactive constituents is a particularly important type of synergism that is underestimated by Science [23], found that the substance genistein increased the levels of epigallocatechin-3-gallate (EGCG) in the small intestine and in the plasma after its oral administrations in mice. Likewise, the combination of decosahexaenoic acid (DHA) (10 μ M) with curcumin (10 μ M) significantly increased curcumin uptake in SK-BR-3 human breast cancer cells, possibly by altering the lipid composition of the membrane [24].

A notable event is what was discovered on the co-administration of piperine and curcumin by this interaction raises plasma curcumin levels by 2000% in humans, and 154% in rats. This may be a result of inhibition of curcumin glucuronidation by piperine, as it is heavily metabolized to glucuronide conjugates before reaching the plasma, and piperine is a well-known inhibitor of hepatic glucuronidation [25].

Synergisms that reduce adverse effects

A unique type of synergy between active molecules is what occurs when one of them acts simply to inhibit or minimize the adverse effect of the Other [26]. Some authors do not consider this type of combination as a synergistic effect, as only one of its components can produce a response, while the other merely reduces the adverse effect of the first without affecting its activity on the target [27]. Most chemotherapeutic drugs, although successful in the treatment of tumor cells, express high adverse effects against healthy cells. In a current study, an extract of staghorn sumac (*Rhus hirta* (L.) Sudw. (Anacardiaceae)) was combined with the antineoplastic 5-fluorouracil (5-FU) commonly used in breast and colon cancer [28].

Synergism against drug resistance mechanisms

Infectious diseases such as those caused by fungi, viruses and bacteria are becoming more difficult to treat due to the development of drug resistance [29-31]. Bacterial resistance, for example, can occur for three reasons: modification of the active site resulting in inefficient drug binding, metabolism of the antibiotic into inactive forms, and efflux of antibiotics out of the bacterial cell [32]. Clinical therapeutic options for infections with highly resistant pathogens as well as new emerging infectious diseases remain limited due to lack of adequate drugs. The development of new therapies cannot, in many cases, adapt to the rapid evolution of these pathogens. Therefore, synergistic pharmacological therapies present a new challenge to more quickly identify new drugs, and/or drug combinations applicable to these prominent infections [33].

In a recent study it was found that dichloromethane extract from the leaves of the shea butter tree (*Vitellaria paradoxa* CF Gaertn. (Sapotaceae)) synergized ampicillin, oxacillin and nafcillin activity against methicillin resistant *Staphylococcus aureus* targeting beta-lactamase enzymes [14].

Synergism between plant extracts

In Chinese herbal medicine, blending plant extracts has been used for over 1000 years to promote health and treat various ailments in China and other Asian countries. The Chinese combine various herbs in order to improve the effectiveness of the active constituents and/or minimize the adverse effects associated with the treatment. The complexity of such formulations represents a major challenge for researchers trying to validate the effectiveness of herbal preparations [34].

Synergism between isolated compounds

Using in vitro methods, curcumin (*Curcuma longa*) combined with piperine (*Piper nigrum* L.) obtained significant neuroprotective activity. They were able to protect human neuroblastoma cells (SH-SY5Y) against induced cytotoxicity β -amyloid (A β), a peptide responsible for the spread of Alzheimer's disease. They also prevented fibrillation and oxidative damage, attenuating toxic effects on neural cells, inhibiting and disaggregating fibrils, as well as suppressing ROS Generation [35]. The estrogenic activity of two flavonoids, baicalein (1 μ M) + daidzein (5 μ M) or baicalein (5 μ M) + daidzein (1 μ M) in vitro, has been demonstrated by their strong abilities to stimulate estrogen receptor phosphorylation and transcriptional response element activation to estrogen in mana cells (MCF-7) [36].

Final Considerations

Scientific investigation of natural products is challenging due to their immense complexity and variability. Most efforts devoted to natural product knowledge are typically devoted to reducing complexity and identifying unique active components for drug development. However, given that crude plant extracts, and not unique molecules, are administered for medicinal purposes interactions between constituents may be of great importance for future studies.

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