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Invitro Evaluation of the Anti-Inflammatory Activity of Phloroglucinol and Alpha-lipoic acid

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ABSTRACT

It was decided to test the anti-inflammatory activity of phloroglucinol and alpha-lipoic acid combined in order to evaluate the possibility of a synergistic effect in the battle against inflammation. Both the antioxidant alpha-lipoic acid and the naturally occurring phenolic compound phloroglucinol were investigated by researchers in order to ascertain whether or not they were capable of modulating inflammatory pathways and pathways in vitro. The effects of the combination on numerous inflammatory mediators, including cytokines (TNF-α, IL-1β, and IL-6), prostaglandin E2 (PGE2), and nitric oxide (NO) generation, were assessed by employing human peripheral blood mononuclear cells (PBMCs) that were cultivated. The results demonstrated that these pro-inflammatory markers were greatly reduced following the combination treatment, which may indicate that the combination treatment had a synergistic effect on reducing inflammation. Furthermore, the combination had a considerable impact on inhibiting the activation of nuclear factor-kappa B (NF-κB), which is an essential regulator of inflammation. These findings imply that the combination of phloroglucinol and alpha-lipoic acid could be a feasible therapy method for inflammatory disorders; nevertheless, additional in vivo research are required to establish the efficacy and safety of the combination.

Keywords: *Phloroglucinol, Alpha lipoic acid, Inflammation, Invitro studies*

1. INTRODUCTION

All living things have the ability to inflame themselves as a defense mechanism. The immune system triggers this biological response whenever it detects a possible danger. It is possible for inflammation to be caused by pathogens such as bacteria, viruses, toxins, toxic chemicals, or tissue damage. [1] There is a vast array of infectious agents that can trigger inflammation. Inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) are produced and released by leukocytes that have been activated by these undesirable stimuli. Additionally, these cytokines trigger a cascade of molecular signals. for modulating inflammation, including interleukin-6 receptors (IL-6R) and tumor necrosis factor receptors (TNFR). Metabolic Activated Protein Kinase (MAPK), Nuclear Factor kappa-B (NF-κB), and Janus Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) are some of the intracellular signaling pathways

that can be altered by receptor activation.[2] Interferons, transforming growth factor (TGF), chemokines, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and many other genes are involved in inflammation. The expression of cytokines can be controlled by these transcription factors. Misregulation of signal pathways originating from NF-kB, MAPK, or JAK-STAT is a major contributor to inflammatory, autoimmune, and metabolic diseases. [3][4]

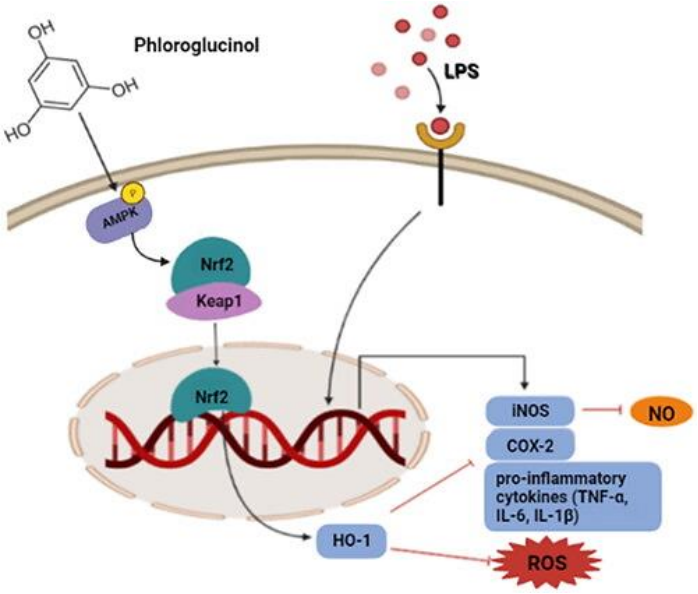

Fig: 1 Phloroglucinol develops anti-inflammatory properties by modulating the AMPK/Nrf2/HO-1 signaling pathway in RAW264.7 murine macrophages that have been activated by lipopolysaccharide (LPS).

Once an acute inflammatory reaction has not been fully eliminated or the healing process has been postponed, it has the potential to transform into a chronic state.[5][6] The reason behind this is that inflammation, whether chronic or acute, is always bad. Recurrent episodes of acute inflammation have the ability to cause chronic inflammation if they happen frequently enough. Chronic inflammation can manifest in different ways, last different amounts of time, and have different effects based on the kind of damage and the body's ability to heal it.[7][8] The main reason for the protracted inflammation is the entry of lymphocytes, macrophages, and plasma cells—mature B lymphocytes that produce antibodies—into the affected tissue. Antibodies are made by plasma cells as well. These cells are withdrawn from circulation due to the progressive release of chemotactic molecules. [9][10] The major cell type in chronic inflammation, macrophages, carry out a variety of functions that lead to tissue damage and the diminished ability to function that follows.

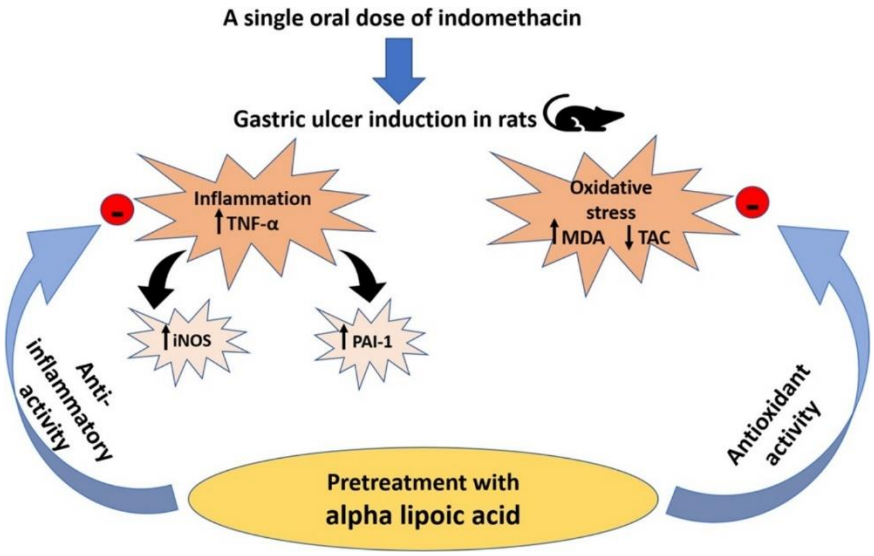

Fig: 2 There is evidence that alpha lipoic acid protects rats from developing stomach ulcers caused by indomethacin.

Anti-inflammatory pharmaceuticals are efficient in lowering inflammation and discomfort. These medications are also known as anti-inflammatory drugs. [12][13] Their assistance can be of use in the treatment of a variety of maladies, including sprains, cramps caused by menstruation, arthritis, and other conditions. [14][15]A small percentage of people may experience unwelcome side effects from taking these medications, despite the fact that the vast majority of people use them without experiencing any adverse effects. Because of the presence of these adverse consequences, there is an increased likelihood that the body will suffer severe damage. Keeping this in mind is absolutely necessary in situations when there are prior health risks. Using these medications requires the utmost caution at all times. It is necessary to be consistent in adhering to dosages that are appropriately controlled. [16][17] Targeting the generation of prostaglandins in order to decrease the ability of cyclooxygenases to produce prostaglandin (PG) E2 for the purpose of finding and developing anti-inflammatory drugs is the primary technique that is utilized. The 5-lipooxygenase (5-LOX) pathway, which is believed to play a role in the synthesis of inflammatory leukotrienes, is also being targeted at the same time as the other pathway. Anti-inflammatory medications can be broken down into two primary categories: nonsteroidal anti-inflammatory medicines (NSAIDs) and corticosteroids. [18][19] Analgesics, antipyretics, and anti-inflammatory treatments are all permitted to be used with nonsteroidal anti-inflammatory drugs (NSAIDs), according to the Food and Drug Administration (FDA). As a result of the absence of these adverse effects, nonsteroidal anti-inflammatory drugs (NSAIDs) can be utilized as an alternative to opioids in the treatment of a wide range of illnesses.[20,21] These conditions include migraines, gout, pyrexia, muscular pain, dysmenorrhea, arthritic disorders, and certain instances of acute trauma. The most common nonsteroidal anti-inflammatory drugs (NSAIDs) are classified by their chemical structure and selectivity as follows: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen), acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam), anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and selective cyclooxygenase-2 (COX-2) inhibitors (celecoxib, etoricoxib). [22][23]. The production of a number of chemical enzymes by our bodies is something that is triggered by inflammation. All of these enzymes are referred to by their abbreviation, cyclooxygenase. There are two different types of COX found in this organism: COX-1 and COX-2. It is the type of COX-1 that generates inflammation that is responsible for the beneficial effects on the health of the lining of your stomach. [24][25] Nonsteroidal anti-inflammatory drugs (NSAIDs) have the ability to decrease the activity of certain COX enzymes. The use of nonsteroidal anti-inflammatory medications (NSAIDs) has proven to be a successful treatment for a wide variety of unpleasant conditions. Some examples of these are sprains, headaches, menstrual pains, and aches and pains in the muscles. The non-steroidal anti-inflammatory drugs (NSAIDs) in question are able to alleviate both types of inflammation because of their lack of selectivity regarding inflammation.[26][27]. Therefore, these medications are efficient in relieving pain; but, they may cause diarrhea or other adverse effects that affect the gastrointestinal tract instead. It is likely that the adverse effects in the stomach are produced by a decrease in COX-1, which serves to protect the mucosa of the stomach and restrict the production of prostaglandins. The likelihood of injuries occurring in patients who have a history of peptic ulcers is significantly higher. In light of the fact that COX-1 and COX-2 stimulate the production of PG, which plays an essential role in the functioning of the kidneys, it is not inconceivable that renal adverse effects could emerge. [28][29].When it comes to people who have adequate renal function, there is very little to no risk associated with restricting the synthesis of PG. When nonsteroidal anti-inflammatory drugs (NSAIDs), which are designed to reduce the production of prostaglandins, are taken by individuals who have renal impairment, complications may occur. Nephrotic syndrome and interstitial nephritis are some of the possible effects that could occur. There is also the possibility of nephrotic syndrome, renal papillary necrosis, electrolyte and fluid imbalances, acute renal failure, and other potential complications. It is possible that people who are taking nonsteroidal anti-inflammatory drugs (NSAIDs) are more likely to experience cardiovascular side effects such as atrial fibrillation, myocardial infarction, and thromboembolic events. It would appear that diclofenac is the nonsteroidal anti-inflammatory drug (NSAID) that is principally responsible for the alarming increase in the number of adverse cardiovascular events that have been recorded. [30][31] It is more frequent for non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) to cause hematologic side effects due to the antiplatelet action they possess. When it comes to patients, this antiplatelet impact is typically only a problem for those who have a history of gastrointestinal ulcers, certain medical diseases (such as hemophilia, thrombocytopenia, von Willebrand disease, and so on), or specific surgical operations. In the event that a patient has a history of adverse responses to [32][33] nonsteroidal anti-inflammatory drugs (NSAIDs), such as urticaria, asthma, or other symptoms that are comparable, or if the patient has a hypersensitivity to salicylates or NSAIDs, it is essential to refrain from using these medications. those individuals who have undergone a coronary artery bypass graft procedure— It is strongly advised that women who are pregnant do not take any nonsteroidal anti-inflammatory drugs (NSAIDS) throughout the second trimester of their pregnancy. After treatment with corticosteroids for an extended period of time, the adrenal glands may gradually stop producing cortisol. It may take some time for the body to return to normal levels of cortisol production after abruptly discontinuing the use of corticosteroids throughout the treatment process.[34] The dangers of corticosteroids are mitigated when they are used for shorter periods of time; however, they are still there. As an example, these drugs have the potential to disrupt the circadian rhythms of a person, which in turn can have an impact on their eating, mood, and sleep. The development of steroid withdrawal syndrome is an additional potential result that may occur. It takes place when the symptoms of the illness that was being treated suddenly return after the medication has been stopped being administered that was being used to treat it. Although it is most frequently associated with oral steroids, it can also be brought on by the use of topical steroids for an extended period of time.[35] Marine bioactive compounds are being investigated by researchers in

the disciplines of biomedicine and nutraceuticals as a possible substitution for their synthetic counterparts that is both safe and effective. One of the sources of phenolic compounds, such as phloroglucinol (PHG), is found in seaweed. These compounds have become quite desirable due to the bioactivities that they possess, particularly in the cosmeceutical and nutraceutical sectors that are found all over the world. PHG has the potential to one day take the place of chemical preservatives because to the effective antioxidant and antibacterial properties that they possess. The phenolic compounds that can be discovered in seaweed are the subject of numerous investigations at the moment. Due to the high antioxidant activity that these compounds possess, it is possible that they will one day be utilized as a substantial therapeutic. One type of antioxidant is caprylic acid, which is often referred to as "alpha-lipoic acid" (ALA) (Figure 3).[36][38] Additionally, it is a component that is produced by the mitochondria, and it is an essential component that assists in the enzymatic digestion of nutrients. It is possible to bring about the neutralization of reactive oxygen species (ROS) through the combination of dihydrolipoate in its reduced form. Reactive oxygen species (ROS) include many types of radicals, such as hydroxyl radicals, superoxide radicals, and radon. In recent times, the antioxidant capabilities of ALA have been brought to the forefront of the discussion in the scientific community. [39]Therefore, it is of great assistance in the treatment of a wide variety of disorders that are associated with oxidative stress, such as radiation injury and ischemia-reperfusion syndrome. In addition, ALA has a wide range of applications in the medical field; it has been shown to be beneficial for patients suffering from altitude sickness, rheumatoid arthritis, Alzheimer's disease, heart nerve difficulties, brain illnesses connected with HIV, diabetic eye problems, and alcoholic liver problems. When looking for a supplement that is made entirely of natural ingredients, it is common to face ALA.[40]

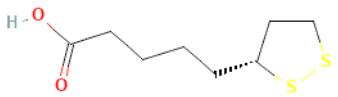

Fig: 3 Structure of alpha-lipoic acid

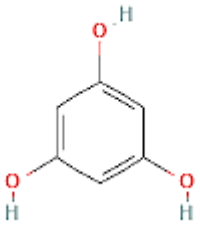

Fig: 4 structure of Phloroglucinol

2. MATERIALS AND METHODS

Invitro studies:

DPPH Activity:

Using a modified quantitative DPPH assay, the anti-oxidant activity level was calculated. To make a DPPH solution, we used "25" HPLC-grade methanol and DPPH (both purchased from Sigma-Aldrich). Each of the three test drugs—PHG, ALA, and PHG+ALA—was plated out in a separate well of a 96-well plate, while the control wells were filled with DMSO. After 30 minutes of incubation, the absorbances were measured at 550 nm to find the percentage of decolorization. Use of vitamin C served as a positive control. Using the Enzfitter® software, we were able to determine the IC50 values, which stand for the concentrations at which 50% decolorization was accomplished.

COX-1 & COX-2 Enzymes inhibitory assay:

Keeping in mind the roles played by these two crucial cyclooxygenases in inflammation, the inhibitory potential of the produced compounds was tested in vitro against COX-1 and COX-2 inhibition. This assessment followed the usual procedure that had been previously defined. The decision was made to prepare the test specimens in increasing concentrations. We also created enzyme solutions for COX-2 (Catalog Number: C0858) and COX-1 (Catalog Number: C0733-5000UN, Sigma-Aldrich), both of which were derived from ovine and human recombinant sources, respectively. On the other hand, COX-2

has a concentration of 300 U/mL and COX-1 is present in concentrations of 0.7–0.8 g/L. The specific enzymes have been tested using Sigma-Aldrich products linoleic acid (CAT: 60-33-3) and arachidonic acid (CAT: 150384). With a concentration of 300 U/mL, the COX-2 enzyme solution was produced. Fifty microliters of the necessary co-factor solution was added to ten microliters of the enzyme solution after it had been heated to four degrees Celsius for five or six minutes. This solution contains 0.9 mM glutathione, 0.24 mM TMPD, and 1 mM hematin. [41][42] With a pH of 8.0 and a concentration of 0.1 M, the Tris buffer is being utilized. After that, for five to ten minutes, the solution containing the enzymes (60 µL volume) and the experimental samples (20 µL volume) with varying concentrations were left at room temperature. To start the procedure, 20 microliters of arachidonic acid at a 30 millimolar concentration were also used. For another fifteen minutes, the mixture's temperature was maintained at 37 degrees Celsius. The procedure was appropriately terminated by adding hydrochloric acid after a UV-visible spectrophotometer had been used to measure the absorbance at 570 nm. The absorbance value per unit of time was used in the computation to calculate the percentage of COX-2 inhibition. Celecoxib was also used as the control group's normative variable in this study.[43,44][45]

Statistical Analysis: Means, in addition to the standard error of the mean, are utilized in order to display the data. The Graph Pad Prism software, which was developed in California, United States, was utilized to carry out a one-way analysis of variance (ANOVA) together with Tukey's test for multiple comparisons. The declaration of statistical significance was made when the p-value was within the range of less than <0.05.

3. RESULTS

In-vitro studies:

DPPH:

A comparison was made between vitamin C (STD) and the anti-oxidant activity of PHG, ALA acid, and their combination, as shown in Table 1. When compared to the activity of the medicines alone, the combined anti-oxidant activity was significantly higher (IC50: 5.3±0.2) and on par with that of the standard treatment.

Table 1: Anti-oxidant activity evaluation of PHG, ALA and combination (PHG+ALA) through DPPH assay

Groups	The IC_{50} values in µg/ml
Standard	2.60±0.4
PHG	12.83±0.7
ALA	15.16±0.8
PHG + ALA	5.3±0.2*#

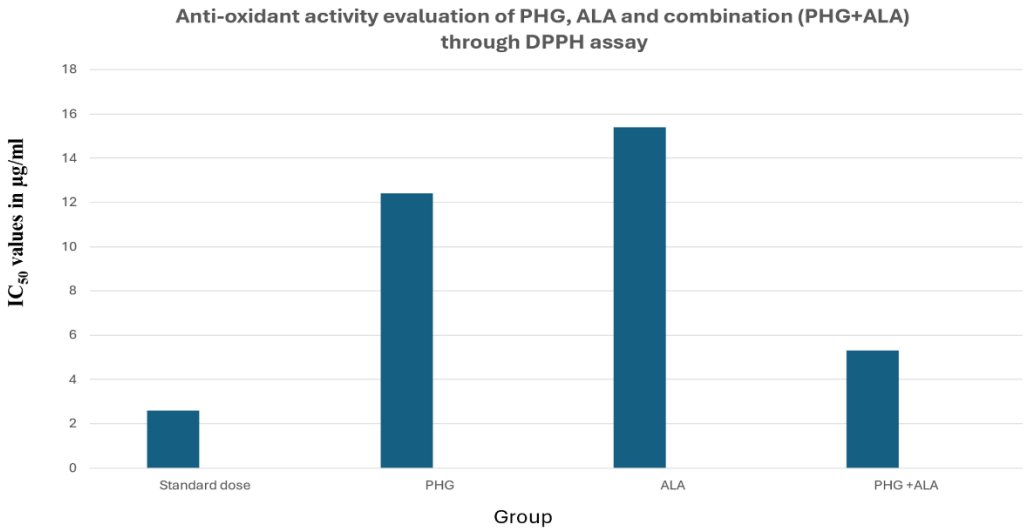

Fig: 5 Anti-oxidant activity evaluation of PHG, ALA and combination (PHG+ALA) through DPPH assay Analysis of anti-inflammatory potential

Table 3: COX-2 inhibitory activity evaluation of PHG, ALA and combination (PHG+ALA) through anti-inflammatory activity assay

Groups	The IC_{50} values in µg/ml
Standard	14.71 ± 0.67
PHG	32.54 ± 0.81
ALA	27.34 ± 1.3
PHG + ALA	19.02 ± 0.40*#

There is a depiction of the data that was obtained from the in vitro COX-1 and COX-2 enzyme inhibition experiment of the compounds that were developed (PHG, ALA) that can be found in Table 2. The selective activity of our medications was directed against the COX-2 enzymes, as opposed to the COX-1 enzymes, which were less selective. On the basis of the results obtained from COX-2, it was concluded that PHG, ALA had the highest degree of efficacy, with an IC50 value of around 14.71 ± 0.67 µM of the compound. Also, it is important to mention that the second highest activity was displayed by PHG, ALA, which had an IC50 value of 32.54 ± 0.81 µM. This is something that should be taken into consideration. The fact that the molecule has a SI value that is relatively high has led to the conclusion that it would be an appropriate option, particularly for individuals who are afflicted with stomach ulcers. The IC50 values that are presented in table 2 demonstrate that each and every one of the medications that we put through our tests was an effective cyclooxygenase-II inhibitor.

4. CONCLUSION

The in vitro investigation of the anti-inflammatory activity of a combination of phloroglucinol and alpha-lipoic acid provides encouraging results, indicating the potential synergistic effects that these two compounds may have in modifying inflammatory responses. A considerable reduction in the generation of pro-inflammatory cytokines, prostaglandins, and nitric oxide was observed as a result of the combination. These three substances are essential mediators in the process of inflammation. Furthermore, the reduction of NF-κB activation provides additional support for the possible anti-inflammatory effects of this combination. Taking into consideration these data, it appears that the combination of phloroglucinol and alpha-lipoic acid could potentially serve as a useful therapeutic method for the management of illnesses connected to inflammation. On the other hand, additional in vivo investigations and clinical trials are required in order to validate the safety, efficacy, and optimal therapeutic dosages of this combination for the purpose of possible clinical applications. The in vitro investigation of the anti-inflammatory activity of a combination of phloroglucinol and alpha-lipoic acid provides encouraging results, indicating the potential synergistic effects that these two compounds may have in modifying inflammatory responses. A considerable reduction in the generation of pro-inflammatory cytokines, prostaglandins, and nitric oxide was observed as a result of the combination. These three substances are essential mediators in the process of inflammation. Furthermore, the reduction of NF-κB activation provides additional support for the possible anti-inflammatory effects of this combination. Taking into consideration these data, it appears that the combination of phloroglucinol and alpha-lipoic acid could potentially serve as a useful therapeutic method for the management of illnesses connected to inflammation. On the other hand, additional in vivo investigations and clinical trials are required in order to validate the safety, efficacy, and optimal therapeutic dosages of this combination for the purpose of possible clinical applications.

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