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RESEARCH ARTICLE

REPOSITION OF GALLOYL DERIVATIVE/ GALLATE EQUIVALENT CLASS OF MOLECULE(S) AS AN ANTI-SARS-COV-2 AND RESPIRATORY MEDICINE OF COVID-19

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ABSTRACT

As galloyl derivative/ gallate equivalent class of molecule(s) were found to have more or less bitter taste and as well as strong antioxidant, antiinflammatory, strong antiproliferative, antimutagenic, anticancer, antitumor, antiulcer, antiischemic, antiatherosclerotic, antidepressive/ antihypertensive, antidiabetic, antimalarial, antiarthritic, immunomodulatory, antiretroviral and anti-human coronavirus (anti-HCoV) like versatile properties as therapeutic as broad spectrum antiviral in the sense of host defensive manner, could be two in one role as it posing a CQ/HCQ like lot of similar functional bioactive- and similar physical bitterness properties or posing a similar structural property with multioxygenated and physically bitter compound like azithromycin (AZM)/ ivermectin (IVM) of anti-SARS-CoV-2 property and the galloyl/ gallate class as bearing similar polyhydroxy/ polyoxygenic type of molecule(s) could be therefore repurposed against novel coronavirus (nCoV) when compared with either bitter CQ/HCQ functionally or AZM/IVM structurally as special references, as well as it can act as a respiratory medicine/ natural ventilator of aerial oxygen by reopening the collapsed air ways of lung in COVID-19 symptomatic patients depending on their strong antioxidantal and antiinflammatory/ immunomodulatory properties so that normal breath/ sufficient aerial oxygen can enter easily when treated. Since the said class of molecule(s) as it possess the strong antiinflammatory property might be involved in decreasing proinflammatory cytokines and/ increasing antiinflammatory cytokines and as well as able to stop the episode of cytokine storm, a key step in ARDS, which was further strengthen by a preliminary study where gallate equivalent enriched *Abroma augusta* leaves hydroalcoholic extract (AALHAE) (50%) and AALHAEplus (50%) has been implemented on a few covid-19 suspected moderate and severe symptomatic patients respectively from my Institute, a promising result was thus obtained. I believe from my experience that the gallate eqv enriched AALHAE/ AALHAEplus may have tremendous role on controlling distress of lung which is used to be damage-targetted by SARS-CoV-2 in serious symptomatic cases.

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INTRODUCTION

The COVID19 pandemic: The coronavirus pandemic is an ongoing global pandemic of coronavirus disease 2019 (COVID19), caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV2) (1). The outbreak was first identified in December 2019 in Wuhan, China (2,3). The World Health Organization declared the outbreak a Public Health Emergency of International Concern on 30th January 2020 and a pandemic on 11 March (4,5). As of 04 January 2021, the total number of global (192 countries) coronavirus confirmed cases has topped 104.3 million, while the total deaths have surged to more than 2.27 million, according to the Johns Hopkins University (6). **Detrimental consequence of COVID-19:** The clinical features of COVID-19 can range from asymptomatic cases to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction. Severe symptoms and lung disorder are co-associative phenomenon. The disease can progress to pneumonia, respiratory failure and death when severe and in this case, acute complications include acute lung injury, ARDS, sepsis and shock.

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This progression is thought to be related to excessive increase in proinflammatory cytokine levels (7,8) leading to a cytokine storm. Since, COVID-19 positive patients are of four types: asymptomatic, mild-, moderate- and severe symptomatic. Moderate symptomatic patient shows common symptom like "feeling of unwell" due to salient hypoxia. Whereas severe symptomatic patient shows severe acute respiratory syndrome (SARS), also called acute respiratory distress syndrome (ARDS) resulting shortness of breath occurs. In both the cases to overcome these problems need oxygen. Since ARDS is directly proportional to the inflammation of lung as an immediate emergent of cytokine storm, an ultimate inflammatory consequence. Due to tremendous inflammation, all the air gate of lung has been collapsed leading to an ultimate death. Anders Kjellberg *et al*. 2020 (9), in the introduction part of his hypothesis described clearly about an outline mechanism of cytokine storm that SARS-CoV-2 affects part of the innate immune response and activates an inflammatory cascade stimulating the release of cyto- and chemokines, particularly within the lung (10,11). The export of such factor attracts neutrophils and monocytes to the site of infection, infiltrating the organ. Unfortunately neutrophils are particularly inefficient to clear the viral infections, and their presence may be more detrimental than beneficial due to the release of a battery of caustic agents directed to kill the pathogen, but they could also damage the surrounding tissue (12).

The destruction of host cells may release subcellular elements that could trigger secondary inflammatory reactions. Thus, SARS-CoV-2 infection activates a robust inflammatory response that if it is not controlled, could result in a "cytokine storm" with detrimental systemic consequences (13). Indeed, the inflammatory response during COVID-19 is likely the cause for the development of acute respiratory distress syndrome (ARDS) in patients, which is a condition of very low arterial oxygen concentration or hypoxia and bilateral pulmonary opacities (14). Even patients that have mild symptoms and survived COVID-19 displayed significant changes on pulmonary CT-scan, with diffuse ground-glass opacities, crazy-paving patterns, and consolidation, suggesting a severe inflammatory involvement (15). Sad story is, no specific antiviral drug is developed as of yet for covid-19 positive patients though vaccination has been started recently which is not enough for global demand.

Galloyl derivative/ gallate equivalent class of molecule(s): Gallic acid is a natural phenolic compound found in several fruits and medicinal plants (16). Gallic acid (3,4,5-trihydroxybenzoic acid), found in many plants either in free form or part of tannins (17). Tannic acid is a specific form of tannin**,** a type of polyphenol. Its weak acidity **(**pK_a around 6) is due to the numerous phenol groups in the structure. The chemical formula for commercial tannic acid is often given as $C_{76}H_{52}O_{46}$, which corresponds with decagalloyl glucose, but in fact it is a mixture of polygalloyl glucoses or polygalloyl quinic acid esters with the number of galloyl moieties per molecule ranging from 2 up to 12 depending on the plant source used to extract the tannic acid (18). *In vitro* antiproliferative activity against ten human cancer cell lines of a series of galloyl derivatives bearing substituted-1,3,4-oxadiazole and carbohydrazide moieties has been reported (19). Epigallocatechin also known as epigallocatechin-3-gallate (EGCG), is the ester of gallic acid present in tea (20).

Antiinflammatory/ Antiarthritic/ Immunomodulatory/ antioxidant effects: Gallic acid was found to possess antiinflammatory activity towards zymosan-induced acute foot pad swelling in mice with via the functioning of polymorphonuclear leukocytes (PMNs) (21). Niloofar Kahkeshani *et al*., 2019 discussed in his review article (16) that gallic acid can extinguish the flames of inflammation via different mechanisms. It decreases the expression and release of proinflammatory and inflammatory mediators, such as bradykinin, substance P, COX-2, PGE-2, NF-κB, IL-2, IL-4, IL-5, IL-6, IFN-γ, and TNF-α. The compound also inhibits the phagocyte- or PMN-mediated inflammatory responses by scavenging ROS and decreasing the myeloperoxidase (MPO) activity (21-26). Also acts as analgesic (24). Gallic acid and its semi-synthetic esters can suppress TNF-α induced NFκB activity could be a chemopreventive in carcinogenesis (17). Nazir N *et al*., 2007 reported: Bergenin, a C-glycoside of 4-O-methyl gallic acid, isolated from rhizomes of *Bergenia stracheyi* (Saxifragaceae) and its O-demethylated derivative norbergenin, prepared from bergenin, are reported to show antiarthritic activity through possible modulation of Th1/Th2 cytokine balance. Flow cytometric study showed that the oral administration of bergenin and norbergenin inhibit the production of proinflammatory Th1 cytokines (IL-2, IFN-γ and TNF-α) while as potentiate antiinflammatory Th2 cytokines (IL-4 and IL-5) in the peripheral blood of adjuvant-induced arthritic balb/c mice. This shows the potential Th1/Th2 cytokine balancing activity of bergenin and norbergenin which is strongly correlated with their antiarthritic activity (22). Effects of methyl gallate (MG) and gallic acid (GA) were reported to inhibit significantly the production of inflammatory cytokines/ mediators of IL-6 and IL-8 gene and protein levels in a dose-dependent manner in oral epithelial cells stimulated with *Fusobacterium nucleatum***.** These compounds also inhibited the growth of *F. nucleatum* (27). MG and GA can inhibit oral bacteria also (28). The antioxidant properties of gallic acid and allied compounds are examined on animal fats, that are protected/ stabilized by antioxidants like di- and poly-phenolic inhibitors (29). Vitamin C equivalent antioxidant capacity (VCEAC) of phenolic phytochemicals also has been reported where gallic acid showed highest relative VCEAC value (30).

Pharmacological/ therapeutical properties: Gallic acid (3,4,5-trihydroxybenzoic acid) is a polyphenol that possesses a wide spectrum of important pharmacological properties. Marciane Maximo da Silva addressed in the introduction section of his research article that in particular, gallic acid affects several pharmacological and biochemical pathways and has strong antioxidant, antiinflammatory, antimutagenic and anticancer properties. Author also reported about a methyl gallate from the methanol extract of *Schinus terebinthifolius* leaves as galloyl group derivatives showing as antitumor agents. Synthesis and *in vitro* antiproliferative activity evaluation of a series of galloyl derivatives were reported by the author first time (19). Mohamed Abdel-Aziz and Amira M Gamal-Eldeen mentioned in the introduction section of their research article 2009 that 2-Pyrazoline derivatives have been reported to exhibit various pharmacological activities such as antimicrobial, antiinflammatory, antihypertensive, antidepressant, and monoamine oxidase inhibitory activities. Similarly, phenolic derivatives such as gallocatechin, epigallocatechin, and caffeic acid, besides their analogs that contain several hydroxy groups on the phenyl moiety, were found to exhibit various useful properties including radical scavenging, antiviral, antioxidant, antiinflammatory, antiatherosclerotic properties, anticancer, heart protecting, and strong topoisomerase inhibiting activities. The study gathers the two bioactive entities (pyrazoline and galloyl moiety) in one compact structure to obtain galloyl pyrazoline derivatives. The prepared compounds (A novel series of galloyl-2-pyrazoline derivatives were synthesized) and were screened by the authors for their anticancer, antioxidant, and antiinflammatory activities (31). Gallic acid has been reported in a review by Naira Nayeem *et al*., 2016, to elicit various biological activities such as antibacterial, antifungal, antiviral, antiinflammatory, antioxidant, anticancer, antidiabetic, antiheartischemic, antiulcer, antimalarial etc. Due to these activities gallic acid could be considered as a promising lead compound for new drug development (32).

Galloyl/ gallate class of molecule(s) as respiratory medicine: An european patent claims physiological tannin extracted from banana stem can be utilized as smockers' candy (33). Antimicrobial and antitubercular activities of some novel synthetic trihydroxybenzamido azetidin-2-one galloyl derivatives has been reported (34). Gallic acid (35) and its analogs (36) inhibits histamine release and proinflammatory cytokine production in mast cells. Protective effects of gallic acid were reported against lung-, heart- and renal fibrosis (37, 38, 39) which were commonly found in covid-19 induced kawasaki (40) and multisystem inflammatory syndrome (MIS) (41) diseases in a rare but serious complication when associated with COVID-19 in infants below 5 years. Also multiorgan fibrosis including lung in adults are common in most severe COVID-19 cases of old age, male sex and comorbidity leading to a multiorgan failure and death (42).

Antiviral property of galloyl/ gallate class of molecule(s): Hydroxybenzoic acids with more free –OH groups on the phenol ring were found more potent against the human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (43-47). Anti-HSV-1 and anti-HIV-1 activity of gallic acid and pentyl gallate were reported by Jadel Müller Kratz *et al*., 2008 **(**48**).** Gallic acid can inhibit HIV-1 integrase, HIV-1 transcriptase, HIV-1 protease dimerization (49-53), HCV attachment and penetration, HCV replication, HCV serine protease (54-57), the herpes simplex virus (HSV)-1 and HSV-2 attachment and penetration (58). It also causes disruption in Haemophilus influenza A and B particles (59). Interestingly HIV (-1/2), HCV and Haemophilus influenza A & B all are enveloped virus possessing single stranded RNA as genetic material (60) which are very much similar to SARS-CoV-2, whereas exception is HSV (-1/2), though it is an enveloped virus but contains a large double stranded DNA genome (61). Among the phenolic acid constituents in *Sambucus formosana* Nakai extract, caffeic acid, chlorogenic acid and gallic acid, all the three are hydroxy phenol moity containing compounds sustained the anti-HCoV-NL63 activity and the results revealed that *Sambucus formosana* Nakai stem ethanol extract displayed the strong anti-HCoV-NL63 potential (62).

Human coronavirus NL63 (HCoV-NL63) is a member of the family *Coronaviridae*, genus *Alphacoronavirus*, and was first discovered in 2004 (63). HCoV-NL63 is mainly associated with the common cold/ severe acute respiratory illness in children, the elderly, and immunocompromised patients (64), which also associated with lower respiratory tract symptoms in infants (65) with SARS-CoV-2, a great similarity found as belonging to the same *coronaviridae* family and using the same type of receptor ACE-2 in infection. Recently, Smarajit Maiti *et al*., 2020 reports a bioinformatics and molecular docking study on epigallocatechin gallate (EGCG) and theaflavin gallate which shows significant interaction with receptor binding protein (ACE-2) and as well as binds throughout SARS-CoV-2 spike-protein central channel at three positions with special reference to the HCQ (66) indicating both the gallate may inhibit SARS-CoV-2 entry/ infection. Gallic acid (3,4,5-trihydroxybenzoic acid), found in many plants either in free-form or part of tannins (17). Gallic acid and galloyl derivative like catechin, tanin, tanic acid (poly galloyl moity) etc. are more/ less bitter and/ astringent in taste (67) like physically bitter montelukast (MLK)/ levocitirizine (LCZ) like antiallergic medications (68) or antimalarial and antiarthritic bitter drug of chloroquine (CQ)/ hydroxychloroquine (HCQ) (68) or multioxygenated (69,70) bitter (71,72) compound of AZM (69,71)/ IVM (70,72) like anti-nCoV (73,74,75). It is clear to say AZM (69) has 12 and IVM (70) has 14 oxygen atoms in their respective structure and both AZM (71) and IVM ((72) are physically bitter in taste. Also AZM has broad spectrum antiviral including anti-SARS-CoV-2 property and antiinflammatory activity (73) and IVM inhibits *in vitro* replication of SARS-CoV-2 (74) and *in vivo* worth a shot (75). Also galloyl class of molecule(s) as posing CQ/HCQ like miscellaneous biological properties of antimalarial, antidiabetic, antihyperlipidemic/ antihypertensive, antiarthritic/ antiinflammatory, immunomodulatory etc. (shown in INTRODUCTION and Table 1 of RESULT section of DOWNLOAD PDF of Ref. 76), clearly indicating galloyl/gallate class of molecule(s) may have functionally CQ/HCQ like anti-SARS-CoV-2 activity as both CQ and HCQ can inhibit SARS-CoV(2003) and SARS-CoV-2(2019) before and after infection has been reported (77) and structurally AZM/IVM like anti-SARS-CoV-2 activity as it bears similar physical property of bitterness and structural property of multioxygenated compound.

MATERIALS AND METHODS

This reposition hypothesis of Galloyl derivative/ gallate equivalent class of molecule(s) as an anti-SARS-CoV-2 when compared with functionally CQ/HCQ and structurally AZM/IVM like multioxygenated compound and as well as simultaneously might be a possible respiratory medicine/ natural ventilator of aerial oxygen in the lung of COVID-19 symptomatic patients, that was retrieved using the database from Google Scolar, PubMed and wider internets. Construction of the hypothesis is supported and discussed with relevant reference/ data collected from existing literatures including one of my recently published Research Article in IJCRT journal (76), all of which were reviewed and meta-analysed. A preliminary study was conducted to test the hypothesis partially at my Institute has been reported (76). Future plan is there for implementation to validate/ verify the hypothesis fully.

RESULTS OF IMPLEMENTATION

It is pertinent to say, from my Institute to test the hypothesis, a preliminary study was conducted on COVID-19 suspected symptomatic patients with some gallate equivalent enriched hydroalcoholic herbal extract and a promising result was obtained (shown in Table 3 of Ref. 76) that has been recently published in IJCRT journal July 2020 (76). Where, in case of moderate symptomatic patients, mild respiratory distress/ feeling of unwell due to silent hypoxia were treated successfully by administering orally with the 50% ethanol extract of decoction of Indian traditional herb, *Abroma augusta* Linn. (Indian Ulatkambal) leaves (collected from Institute garden), also called AALHAE. Preparation and Dose were described in the Method section of my recent publication (76).

Apart from this, in case of homeopathy *Abroma augusta* mother tincture was used via oral administration frequently, no toxicity was reported ever. In case of suspected severe symptomatic patient, respiratory distress were controlled with the hydroalcoholic (50%) leaf-extract of the same herb *A. augusta* (total phenolic+flavonoid content=15.76+/-0.16 mg GAE/g leaf) (78) of which antiinflammatory and/ antiasthmatic activities were increased by adding *Osimum sanctum* leaves (the total phenolic content=50.2+/-0.6mg gallic acid/g sample) (79), *Zingiber officinale* (phenolic content was measured=61.5+/-5.27mg GAE/g in 70% hydroalcoholic ginger extract) (80), black tea (the polyphenol content 17.62+/-0.42mg GAE/g) (81) and *Piper nigrum* (total phenolic+flavonoid content 32.83+/-0.0mg GAE/g of dry extract (82). The polyherbal formulation (PHF) was thus called AALHAEplus {therefore, all total GAE in AALHAEplus=(15.76+/-0.16)+(50.2+/-0.6)+(61.50+/-5.27)+(17.62+/-0.42)+ (32.83+/-0.0)}=177.91+/-6.45mg/g, therefore, ratio of GAE of AALHAEplus and that of AALHAE=(177.91+/-6.45)÷(15.76+/-0.16)=>177.91 ÷ 15.76 (for simplicity of division, ignoring +/-6.45 and +/-0.16)= 11.3 (approx.) times more stronger antioxidant and antiinflammatory properties belongs to AALHAEplus than AALHAE depending on GAE content, though the figure is not real in this 50% hydroalcoholic extract but estimation guessing from existing literature. In no case, oxygen cylinder and/ inhaler and/ nebuliser was/ were required. *A. augusta* leaves are enriched with high level of quercetin, ascorbic acid and gallic acid equivalents (78) like strong antioxidants, antiinflammatory, antiproliferative, antimutagenic and anticancer (19) and important elements like cobalt, nickel, iron, calcium and magnesium (83,78). Apart from this, I can say I have long experience on AALHAE/ AALHAEplus hebal formulations, which I implemented on more than 100 old asthma patients, more than 90% of which were get rid of this ailment permanently, except few COPD asthma (data preserved for patent filing). But recently reported that GA is even effective against COPD (84).

DISCUSSION

Depending on the said antiinflammatory/ immunomodulatory action and other profound versatile diversity in biological/ therapeutic activities like antioxidant, antiproliferative, antimutagenic, anticancer, antitumor, antiulcer, antidiabetic, antidepressant/ antihypertensive, antiartherosclerotic, etc., properties (32,16,85) of galloyl/ gallate class of molecule(s), which may have link directly/ indirectly controlling over the consequence of inflammation web, I would like to emphasise that galloyl/ gallate class of molecule(s), may be effective in such silent hypoxia in moderate and SARS/ARDS in severe COVID-19 symptomatic patients as evident from the role of bergenin/ norbergenin type of galloyl derivatives in inhibiting the production of proinflammatory cytokines as well as promoting the antiinflammatory cytokines (22) may stop the ultimate cytokine storm episode which was also further strengthen by implementation results of gallate equivalent from *A. Augusta* from my Institute. Though AALHAE/ AALHAEplus was applied throuh oral route (76), but question is GAE present in *A. Augusta* leaf were really absorbed intact molecular form or digested form of gut yet not been studied except in black tea (86) a component of AALHAEplus that was added and also in other report *in silico* study revealed that the compounds of some synthetic galloyl derivatives showed good intestinal absorbtion (19). The absorption, distribution, metabolism, and excretion (ADME) properties of the such compounds was performed by investigating their match of Lipinski's rules, topological polar surface area (TPSA) and percentage of absorption (%ABS) study (19). Further more detailed studies are required with other models, such as *in vivo* assays/ implementing on moderate and/ severe symptomatic COVID-19 positive/ confirmed patients, are essential for the characterization of these derivatives/ equivalents as a ventilating agent either by purifying/ crude fractionation of the said herbs or from synthetic/ devised one. Moreover, I believe these gallolyl/ gallate class of miracle molecule(s) may inhibit SARS-CoV-2 as they have lot of functional similarities with CQ/HCQ, though structurally disimilar with the same CQ/HCQ but the structural similarities with azithromycin/ ivermectin a multi oxygenated compounds; all of them

have established anti-SARS-CoV-2 potential and as well as can challenge/ improve the oxygen demanding situation due to SARS/ ARDS arisen in severe symptomatic COVID-19 patients during oxygen cylinder scarcity in hospitals in highly populated countries like Brazil/ India, where it may act as an unique, highly potent strong antiinflammatory and may be likely to be more better and tight safe when it was implemented in combination with two bitter antiallergic medications (MLK+LCZ) and bitter AZM along with CBTT model of treatment and instant effective against cytokine storm as I found in suspected symptomatic cases (76). In my opinion, since the phenolic and flavonoids, so called gallic acid equivalents are secondary metabolites (87) of plant which are providing them host defence against plant pathogen including life threatening viruses, therefore, the said class of molecule(s) may be able to maintain oxygen homeostasis/ balance in other organism like human body also as we aware of too much/ too low level of oxygen may create pathophysiological condition (88).

Though this class of molecule(s) does not prove that it is an alternative source of oxygen as being multihydroxylated/ multioxygenated compound but being a strong antioxidant, antiinflammatory/ immunomodulatory, it may tackle the detrimental effect of cytokine storm. It should be noted here, hyperbaric oxygen serves safely as an antiinflammatory treatment in COVID-19 (9). Apart from, it could be mentioned; plant polyphenol, tannin, -a large quantities present in food and beverages (tea, red wine, nuts, etc.) exert broad cancer chemoprotective in animal models (89) also as we know TNF-α, a proinflammatory cytokine involved in agressive growth of tumor, can be supressed by gallic acid and its derivative (17). Though remember it, malignant tumor/ cancer is not an inflammation but inflammation always associated along with infection. COVID-19 initially an influenza like acute injury induced by SARS-CoV-2. Inflammatory allergic diseases such as, asthma, allergic rhinitis, and sinusitis is a very important issue in human health specially in pandemic situation. Gallic acid (3,4,5-trihydroxybenzoic acid), a polyphenol natural product from gallnut and green tea, is known to have antioxidant, antiinflammatory, antimicrobial, and radical scavenging activities. Gallic acid inhibits immunoglobulin E (IgE)-induced histamine release and proinflammatory cytokine expression derived from mast cells. Antiallergic effect of gallic acid suggests a possible therapeutic application of this agent in inflammatory allergic diseases (35). Gallic acid also can act as antifibrotic in severe COVID-19 cases (37-39). Therefore, I can conclude; on the basis of antiallergic, antifibrotic, antiinflammatory and antioxidantal concern including vitamin C like activity of the galloyl/ gallate class of molecule(s) could be a respiratory medicine in COVID-19 crisis, releaving respiratory distress likely to be acting as a natural ventilator of aerial oxygen, attenuating inflammation in lung by its antihistaminic/ antiallergic (35,36) and antiinflammatory/ immunomodulatory (21-26) role, also the ventilation property of such class of molecule(s) which could be proved as evident from recent report of reduced inflammation that was accompanied with normalization of redox balance as reflected by effects of GA against COPD-linked lung inflammation/ emphysema in elastase and cigarette smoke-induced mice (84) and as well as depending on its versatile pharmaceutical-, broad spectrum antiviral activities including recently reported EGCG and theaflavin, the main two active ingredients of green tea and black tea, respectively, showed potential inhibitory activity against the SARS-CoV-2 3CL-protease in a dose-dependent manner *in vitro* (90) and computational study indicated polyphenols of pomegranate peel extract as potential inhibitor of SARS-CoV-2 internalization (91) and depending on physical property of more/ less bitter taste, it is rational to say; it could be an alternate anti-SARS-CoV-2 therapeutics when compared functionally with bitter CQ/HCQ and structurally with bitter tasted AZM/IVM. From literature it has also been found that total phenolic content of essential oil of lemon leaf was 14.73 mg gallic acid equivalent/g dry plant material (92). Peels of grapefruit had the highest total phenolic content followed by lemon and orange, which was found to be 77.3, 49.8, and 35.6 mg of gallic acid equivalent/g of peels, respectively (93). Though the lemon leaf (92) and peels of grapefruit, lemon and orange (93) were not added to AALHAEplus as prepared from my Institute (76).

Conclusion

As I got magic result when treated few suspected symptomatic patients including one of them suffering from pre-existing asthma with combination therapy of AALHAE/ AALHAEplus, + spc. allopathic medications like AZM and + antiallergic medications (MLK+LCZ) etc. (Table 3, Ref.76). At present trial is running initially at my Institute level with crude AALHAE/ AALHAEplus on confirmed COVID positive patients along with the same spc. allopapathic medications. Latter attempt will be taken with AALHAE/ AALHAEplus alone without spc allopath medications. Therefore, need to further study to identify active purified gallate equivalent component from *A. Augusta* leaf extract, as I am ready to send a project at government level. I believe the single molecule future curative/ game changer of present covid crisis belongs to the such class of molecule(s). Unambiguously I can say, this is the universal defence class of molecule(s) which not only repurposing against SARS-CoV-2 and possible respiratory medicine of COVID-19 but also can challenge emerging/ upcoming new new viruses showing without any adverse side effects as phytomedicine.

Author contributions

This study was conceptualized, original draft writing, editing, hypothesising, literature reviewing and meta-analysis were done by author himself.

Conflict of Interest: There is no conflict of interest except patent.

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REFERENCES

1. "Naming the coronavirus disease (COVID-19) and the virus that causes it" World Health Organization, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.
2. Novel coronavirus-China, World Health Organization, https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/.
3. Chaolin Huang, Prof, MD *et al*., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet*, 2020, 395(10223), 497–506, doi: 10.1016/S0140-6736(20)30183-5, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7159299.
4. World Health Organization: Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV); https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov).
5. World Health Organization; https://en.m.wikipedia.org/wiki/World_Health_Organization.
6. "COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU), Coronavirus Resource Centre, Total confirmed and death cases, https://coronavirus.jhu.edu/map.html.
7. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutierrez-Ocampo E, Villamizar-Pena R, Holguin-Rivera Y, Escalera-Antezana JP, Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis, *Travel Med Infect Dis*, 2020, 101623, PubMed PMID: 32179124. Epub 2020/03/18. Eng, (PMC free article) (PubMed) (Google Scholar).
8. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China, *Allergy*, 2020, Pub Med PMID: 32077115. Epub 2020/02/23. eng. (PubMed) (Google Scholar)

9. Anders Kjellberg, *et al*., Can Hyperbaric Oxygen safely serve as an antiinflammatory treatment for COVID-19?, *Med Hypothesis*, published online 30 August, 2020, 110224, in press, Journal Pre-proof, https://www.sciencedirect.com/ science/article/pii/ S0306987720314444?dgcid=raven_sd_aip_email.
10. S Perlman, J Netland, Coronaviruses post-SARS: update on replication and pathogenesis, *Nature reviews Microbiology*, 2009, 7, 439-450, (View Record in Scopus) (Google Scholar).
11. R Channappanavar, S Perlman, Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology, *Semin Immunopathol*, 2017, 39, 529-539, (View Record in Scopus) (Google Scholar).
12. B Drescher, F Bai, Neutrophil in viral infections, friend or foe? *Virus Res*, 2013, 171, 1-7, Article Download PDF (View Record in Scopus)(Google Scholar).
13. YR Guo, QD Cao, ZS Hong, YY Tan, SD Chen, HJ Jin, *et al*., The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status, *Mil Med Res*, 2020, 7, 11, (View Record in Scopus) (Google Scholar).
14. JG Wilson, CS Calfee, ARDS Subphenotypes: Understanding a Heterogeneous Syndrome, *Critical care* (London, England), 2020, 24, 102, (View Record in Scopus) (Google Scholar).
15. F Pan, T Ye, P Sun, S Gui, B Liang, L Li, *et al*., Novel Coronavirus (COVID-19) Pneumonia, *Radiology*, 2020 (2019), Article 200370, (Google Scholar).
16. Niloofar Kahkeshani, *et al*., Pharmacological effects of gallic acid in health and diseases: A mechanistic review, *Iran J Basic Med Sci*, 2019, 22(3), 225–237, doi: 10.22038/ijbms.2019.32806.7897, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6528712/.
17. Mauro Cesar Cafundo da Morais, *et al*., Suppression of TNF-α induced NFκB activity by gallic acid and its semi-synthetic esters: Possible role in cancer chemoprevention, *Natural product research*, 2010, 24(18), 1758-1765, DOI: 10.1080/14786410903335232, https://www.researchgate.net/publication/43227922_Suppression_of_TNFa_induced_NFkB_activity_by_gallic_acid_and_its_semi synthetic_esters_Possible_role_in_cancer_chemoprevention.
18. Tannic acid; https://en.m.wikipedia.org/wiki/Tannic_acid.
19. Marciane Maximo da Silva, Marina Comin,Thiago Santos Duarte, Mary Ann Foglio, João Ernesto De Carvalho, Maria Do Carmo Vieira, and Anelise Samara NazariFormagio, Synthesis, Antiproliferative Activity and Molecular Properties Predictions of Galloyl Derivatives, *Molecule*, 2015, 20(4), 5360-5373, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6272127/#__ffn_sectitle.
20. Epigallocatechin_gallate; https://en.m.wikipedia.org/wiki/Epigallocatechin_gallate.
21. Kroes B.H., van den Berg A.J.J., Quarles van Ufford H.C., van Dijk H., Labadie R.P. Anti-inflammatory activity of gallic acid. *Planta Med*, 1992, 58, 499–504, doi: 10.1055/s-2006-961535. (PubMed) (CrossRef) (Google Scholar).
22. Nazir N, Koul S, Qurishi MA, Taneja SC, Ahmad SF, Bani Sg, Q azi GN, Immunomodulatory effect of bergenin and norbergenin against adjuvant-induced arthritis: a flow cytometric study. *J Ethnopharmacol*, 2007, 112, 401–405, (Crossref), (PubMed), (Web of Science ®), (Google Scholar).
23. Lamees A. BenSaad *et al*, Anti-inflammatory potential of ellagic acid, gallic acid and punicalagin A&B isolated from Punicagranatum, *BMC Complement Altern Med*, 2017, 17, 47, doi: 10.1186/s12906-017-1555-0, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5237561/.
24. Santos A, De Campos R, Miguel O, Cechinel-Filho V, Yunes R, Calixto J, The involvement of K+ channels and Gi/o protein in the antinociceptive action of the gallic acid ethyl ester, *Eur J Pharmacol*, 1999, 379, 7–17, (PubMed) (Google Scholar).
25. Choi K, Lee Y, Jung M, Kwon S, Kim M, Jun W, *et al*., Gallic acid suppresses lipopolysaccharide-induced nuclear factor-κB signaling by preventing RelA acetylation in A549 lung cancer cells, *Mol Cancer Res*, 2009, 7, 2011–2021, (PubMed) (Google Scholar).
26. Wen L, Qu T, Zhai K, Ding J, Hai Y, Zhou J, Gallic acid can play a chondroprotective role against AGE-induced osteoarthritis progression, J *Orthop Sci*, 2015, 20, 734–741, (PubMed) (Google Scholar).
27. Kang MS, Jang HS, Oh JS, Yang KH, Choi NK, Lim HS, Kim SM, Effects of methyl gallate and gallic acid on the production of inflammatory mediators interleukin-6 and interleukin-8 by oral epithelial cells stimulated with Fusobacteriumnucleatum, *J Microbiol*, 2009, 47, 760–767, doi: 10.1007/s12275-009-0097-7, (PubMed) (CrossRef) (Google Scholar).
28. Kang MS, Oh JS, Kang IC, Hong SJ, Choi CH, Inhibitory effect of methyl gallate and gallic acid on oral bacteria, *J Microbiol*, 2008, 46, 744–750, doi: 10.1007/s12275-008-0235-7, (PubMed) (CrossRef) (Google Scholar).
29. Golumbic C, Mattill HA, The antioxidant properties of gallic acid and allied compounds, *J Am Chem Soc*, 1942, 19, 144–145, (Google Scholar).
30. Dae-Ok Kim, Ki Won Lee, HyongJoo Lee and Chang Yong Lee, Vitamin C Equivalent Antioxidant Capacity (VCEAC) of Phenolic Phytochemicals, *Journal of Agricultural and Food Chemistry*, 2002, 50(13), 3713-3717, https://doi.org/10.1021/jf020071c, https://pubs.acs.org/doi/10.1021/jf020071c.
31. Mohamed Abdel-Aziz and Amira M Gamal-Eldeen, Synthesis and screening of anticancer, antioxidant, and antiinflammatory activities of novel galloylpyrazoline derivatives, *Pharmaceutical Biology*, 2009, 47(9), 854-863, https://doi.org/10.1080/13880200902946452.
32. Naira Nayeem, Asdaq SMB, Heba Salem and Said AHEI-Alfqy, Gallic acid: A promising lead molecule for drug development, *J App Pharm*, 2016, 8(2), DOI:10.4172/1920-4159.1000213.
33. Inventor: Angel Ruiz Gabaldon, Method for obtaining a physiological tannin extract from banana trees and the use thereof as food complement, *European Patent Office*: 2005-09-21, Publication of EP1576892A1, https://patents.google.com/patent/EP1576892A1/en.
34. Ilango K, Arunkumar S, Synthesis, antimicrobial and antitubercular activities of some novel trihydroxybenzamido azetidin-2-one derivatives, *Trop J Pharm Res*, 2011, 10, 219–229, doi: 10.4314/tjpr.v10i2.66567, (CrossRef) (Google Scholar).
35. Sang-Hyun Kim, Chang-Duk Jun, Kyongho Suk, Byung-Ju Choi, Hyunjeung Lim, Seunja Park, SeungHo Lee, Hye-Young Shin, Dae-Keun Kim, Tae-Yong Shin, Sang-Hyun Kim, Chang-Duk Jun, Kyongho Suk, Byung-Ju Choi, Hyunjeung Lim, Seunja Park, SeungHo Lee, Hye-Young Shin, Dae-Keun Kim, Tae-Yong Shin, Gallic Acid Inhibits Histamine Release and Pro-inflammatory Cytokine Production in Mast Cells, *Toxicological Sciences*, 2006, 91(1), 123-131, https://doi.org/10.1093 /toxsci/kfj063, https:// academic.oup.com/toxsci/article/91/1/123/1672576.
36. Xiang Fei, *et al*., Synthesis of Gallic Acid Analogs as Histamine and Pro-Inflammatory Cytokine Inhibitors for Treatment of Mast Cell-Mediated Allergic Inflammation, *Molecules*, 2017, 22(6), 898, doi: 10.3390/molecules 22060898., https://pubmed.ncbi.nlm.nih.gov/28555061/.
37. Nikbakht J, Hemmati A, Arzi A, Mansouri M, Rezaie A, Ghafourian M, Protective effect of gallic acid against bleomycin-induced pulmonary fibrosis in rats, *Pharmacol Rep*, 2015, 67, 1061–1067, (PubMed) (Google Scholar).
38. Sutra T, Oiry C, Azay-Milhau J, Youl E, Magous R, Teissedre PL, *et al*., Preventive effects of nutritional doses of polyphenolic molecules on cardiac fibrosis associated with metabolic syndrome: involvement of osteopontin and oxidative stress, *J Agric Food Chem*, 2008, 56, 11683–11687, (PubMed) (Google Scholar).
39. Yousuf M, Vellaichamy E, Protective activity of gallic acid against glyoxal -induced renal fibrosis in experimental rats, *Toxicol Rep*, 2015, 2, 1246–1254, (PMC free article) (PubMed) (Google Scholar).
40. Kawasaki disease; https://www.mayoclinic.org/diseases-conditions/kawasaki-disease/symptoms-causes/syc-20354598.

41. Multisystem inflammatory syndrome; https://www.cdc.gov/mis-c/.
42. Peter M George, MD, Athol U Wells, Prof, MD, and R Gisli Jenkins, Prof, PhD, Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy, *Lancet Respir Med*, 2020 Aug, 8(8), 807–815, doi: 10.1016/S2213-2600(20)30225-3, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7228727/.
43. Borges A, Ferreira C, Saavedra M, Simoes M, Antibacterial activity and mode of action of ferulic and gallic acids against pathogenic bacteria, *Microb Drug Resist*, 2013, 19, 256–265, (PubMed) (Google Scholar).
44. Cueva C, Moreno-Arribas M, Martin-Alvarez P, Bills G, Francisca Vicente M, Basilio A, *et al*., Antimicrobial activity of phenolic acids against commensal, probiotic and pathogenic bacteria, *Res Microbiol*, 2010, 161, 372–382, (PubMed) (Google Scholar).
45. Farag M, Al-Mahdy D, Salah El Dine R, Fahmy S, Yassin A, Porzel A, *et al*., Structure activity relationships of antimicrobial gallic acid derivatives from pomegranate and acacia fruit extracts against potato bacterial wilt pathogen, *Chem Biodivers*, 2015, 12, 955–962, (PubMed) (Google Scholar).
46. Rivero-Buceta E, Carrero P, Doyagüez E, Madrona A, Quesada E, Camarasa M, *et al*., Linear and branched alkyl-esters and amides of gallic acid and other (mono-, di- and tri-) hydroxy benzoyl derivatives as promising anti-HCV inhibitors, *Eur J Med Chem*, 2015, 92, 656–671, (PubMed) (Google Scholar).
47. Sanchez-Maldonado A, Schieber A, Ganzle M, Structure–function relationships of the antibacterial activity of phenolic acids and their metabolism by lactic acid bacteria, *J Appl Microbiol*, 2011, 111, 1176–1184, (PubMed) (Google Scholar).
48. Jadel Müller Kratz *et al*., Anti-HSV-1 and anti-HIV-1 activity of gallic acid and pentyl gallate, *Mem Inst Oswaldo Cruz*, 2008, 103(5), 437-442, doi: 10.1590/s0074-02762008000500005.
49. Modi M, Goel T, Das T, Malik S, Suri S, Rawat AK, *et al*., Ellagic acid & gallic acid from *Lagerstroemia speciosa* L. inhibit HIV-1 infection through inhibition of HIV-1 protease & reverse transcriptase activity, *Indian J Med Res*, 2013, 137, 540–548, (PMC free article) (PubMed) (Google Scholar).
50. Singh A, Pal T, Docking analysis of gallic acid derivatives as HIV-1 protease inhibitors, *Int J Bioinform Res Appl*, 2015, 11, 540–546, (PubMed) (Google Scholar).
51. Ahn C, Jung W, Park S, Kim Y, Kim W, Je J, Gallic acid-g-chitosan modulates inflammatory responses in LPS-stimulated RAW2647 cells via NF-kappaB, AP-1, and MAPK pathways, *Inflammation*, 2016, 39, 366–374, (PubMed) (Google Scholar).
52. Flausino O, Dufau L, Regasini L, Petronio M, Silva D, Rose T, *et al*., Alkyl hydroxybenzoic acid derivatives that inhibit HIV-1 protease dimerization, *Curr Med Chem*, 2012, 19, 4534–4540, (PubMed) (Google Scholar).
53. Kratz J, Andrighetti-Frohner C, Kolling D, Leal P, Cirne-Santos C, Yunes R, *et al*., Anti-HSV-1 and anti-HIV-1 activity of gallic acid and pentyl gallate, *Mem Inst Oswaldo Cruz*, 2008, 103, 437–442, (PubMed) (Google Scholar).
54. Zuo G, Li Z, Chen L, Xu X, In vitro anti-HCV activities of *Saxifraga melanocentra* and its related polyphenolic compounds, *Antivir Chem Chemother*, 2005, 16, 393–398, (PubMed) (Google Scholar).
55. Govea Salas M, Rivas Estilla A, Morlett Chávez J, Lozano Sepúlveda S, Rodríguez Herrera R, Aguilar González C, P420 gallic acid has antiviral effect against hepatitis C virus (HCV), which is mediated by its antioxidant activity, *J Hepatol*, 2014, 60(1), S208, (Google Scholar).
56. Govea-Salas M, Rivas-Estilla A, Rodriguez-Herrera R, Lozano-Sepulveda S, Aguilar-Gonzalez C, Zugasti-Cruz A, *et al*., Gallic acid decreases hepatitis C virus expression through its antioxidant capacity, *Exp Ther Med*, 2016, 11, 619–624, (PMC free article) (PubMed) (Google Scholar).
57. Hsu W, Chang S, Lin L, Li C, Richardson C, Lin C, *et al*., *Limonium sinense* and gallic acid suppress hepatitis C virus infection by blocking early viral entry, *Antiviral Res*, 2015, 118, 139–147, (PubMed) (Google Scholar).
58. Kratz J, Andrighetti-Frohner C, Kolling D, Leal P, Cirne-Santos C, Yunes R, *et al*., Anti-HSV-1 and anti-HIV-1 activity of gallic acid and pentyl gallate, *Mem Inst Oswaldo Cruz*, 2008, 103, 437–442, (PubMed) (Google Scholar).
59. Lee J, Oh M, Seok J, Kim S, Lee D, Bae G, *et al*., Antiviral effects of black raspberry (*Rubus coreanus*) seed and its gallic acid against influenza virus infection, *Viruses*, 2016, 8(6), 157, (PMC free article) (PubMed) (Google Scholar).
60. RNA virus; https://en.m.wikipedia.org/wiki/RNA_virus.
61. Double-Stranded DNA Virus-Herpesviruses; *Biology Libre Texts*, Aug 15, 2020, https://bio.libretexts.org/Bookshelves/Microbiology/Book%3A_Microbiology_(Boundless)/9%3A_Viruses/9._11%3A_DNA_Viruses_in_Eukaryotes/9.11C%3A_Double-Stranded_DNA_Viruses_-_Herpesviruses.
62. Weng Jing-Ru, Lin Chen-Sheng, Hsueh-Chou Lai, Lin Yu-Ping, *et al*., Antiviral activity of *Sambucus formosana* Nakai ethanol extract and related phenolic acid constituents against human coronavirus NL63, *Virus Research*, 2019 Nov, 273, 197767.
63. Van der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, *et al*., Identification of a new human coronavirus, *Nat Med*, 2004, 10, 368–373, doi:10.1038/nm1024, (PubMed) (Web of Science) (Google Scholar).
64. Van der Hoek L, Pyrc K, Berkhout B, Human coronavirus NL63, a new respiratory virus, *FEMS Microbiol Rev*, 2006, 30, 760–773, doi:10.1111/j.1574-6976.2006.00032.x. (PubMed) (Google Scholar).
65. Kaiser L, Regamey N, Roiha H, Deferent C, Frey, Human coronavirus NL63 associated with lower respiratory tract symptoms in early life. *Pediatr Infect Dis J*, 2005, 24, 1015–1017, doi:10.1097/01.inf.0000183773.80217.12.(PubMed) (Web of Science) (Google Scholar).
66. Smarajit Maiti and Amrita Banerjee, Epigallocatechingallate and theaflavingallate interaction in SARS-CoV-2 spike-protein central channel with reference to HCQ interaction: Bioinformatics and molecular docking study, *Drug Dev Res*, accepted 14 July, 2020, DOI: 10.1002/ddr.21730, https://www.ncbi.nlm.nih. gov/pmc/articles/PMC7436314/.
67. Jane L Robichaud and Ann C Noble, Astringency and bitterness of selected phenolics in wine, *Journal of the Science of Food and Agriculture*, 1990, 53(3), https://doi.org/10.1002/jsfa.2740530307.
68. Dipankar Bhattacharyya, Reposition of montelukast either alone or in combination with levocetirizine against SARS-CoV-2, *Med Hypotheses*, 2020 Nov, 144, 110046, doi: 10.1016/j.mehy.2020.110046, Published online 2020 June 28,https://www.sciencedirect.com/science/article/abs/pii/S030698772031820X, also accepted by WHO, under GLOBAL LITERATURE ON CORONAVIRUS DISEASES, ID: covidwho-627612, https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/en/covidwho-627612.
69. Azithromycin; https://pubchem.ncbi.nlm.nih.gov/compound/Azithromycin
70. Ivermectin; https://pubchem.ncbi.nlm.nih.gov/compound/Ivermectin.
71. Amin F, *et al*., A new strategy for taste masking of azithromycin antibiotic: development, characterization, and evaluation of azithromycin titanium nanohybrid for masking of bitter taste using physisorption and panel testing studies, *Drug Design, Development and Therapy*, 2018, 12, 3855-3866, https://www.dovepress.com/a-new-strategy-for-taste-masking-of-azithromycin-antibiotic-developmen-peer-reviewed-article-DDDT.
72. "Ivermectin has an extremely bitter tastes, some animals may object" available from IVERMECTIN, Mar Vista Animal Medical Center, https://www.marvistavet. com/ivermectin.pml.
73. Nathalie Bleyzac, *et al*., Azithromycin for COVID-19: More Than Just an Antimicrobial?, *Clin Drug Investig*, 2020 Jun, 12, 1–4, doi: 10.1007/s40261-020-00933-3 (Epub ahead of print), https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC7290142/.
74. Leon Caly, *et al*., The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro, *Antiviral Research*, 2020

June, 178, 104787, https://www.sciencedirect.com/ science/article/pii/S0166354220302011.
75. Ivermectin for COVID-19: Worth a shot?; https://www.medpagetoday.com/special-reports/exclusives/88310.
76. Dr. Dipankar Bhattacharyya, Naturally occurring alternative treatment model of chloroquine/ hydroxychloroquine model + azithromycin + antiallergic medications effective in COVID-19 suspected symptomatic patients: An Indian perspective, *Int J Creat Res Thought*, 2020 July, 8(7), 2149-2184, Aricle Download PDF, http://ijcrt.org/viewfulltext.php?&p_id=IJCRT2007194.
77. Katelyn A Pastick, Elizabeth C Okafor, Fan Wang, Sarah M Lofgren, Caleb P Skipper, Melanie R Nicol, Matthew F Pullen, Radha Rajasingham, Emily G McDonald, HTodd C Lee, Ilan S Schwartz, Lauren E Kelly,Sylvain A Lother, Oriol Mitjà, Emili Letang, Mahsa Abassi, David R Boulware, Hydroxychloroquine and Chloroquine for Treatment of SARS-CoV-2 (COVID-19), *Open Forum Infectious Diseases*, 2020, 7(4), ofaa130.
78. P Sunitha, N Sathyanarayana, V C Suresh, S Sreeramanan and R Xavier, Phytochemical and antioxidant analysis of leaf extract of Malaysia medicinal plant *Abroma augusta* L., *Indian J Pharm Sci*, 2018, 80(1), 192-198, https://www.ijpsonline.com/articles/phytochemical-and-antioxidant-analysis-of-the-leaf-extract-of-malaysian-medicinal-plant-iabroma-augustai-l-3443.html.
79. Wantida Chaiyana *et al*., *Ocimum sanctum* Linn. as a natural source of skin anti-ageing, compounds, *Industrial Crops and Products*, 2019, 127, 217-224, https://www.sciencedirect.com/ science/article/abs/pii/S0926669018309543.
80. Abolfazl Aslani, Alireza Ghannadi, and Farnaz Rostami, Design, formulation, and evaluation of ginger medicated chewing gum, *Adv Biomed Res*, 2016, 6, 130, doi: 10.4103/2277-9175.187011, https://www.ncbi.nlm.nih. gov/pmc/articles/PMC4976530/.
81. Claudia Anesini *et al*., Total polyphenol content and antioxidant capacity of commercially available tea (*Camellia sinensis*) in Argentina, *J Agric Food Chem*, 2008, 56(19), 9225-9229. doi: 10.1021/jf8022782. Epub 2008 Sep 6, https://www.researchgate.net/ publication/23243880_Total_Polyphenol_Content_and_Antioxidant_Capacity_of_Commercially_Available_Tea_Camellia_sinensis_in_Argentina 62.
82. Proity Nayeeb Akbar *et al*., Antioxidant capacity of piper longum and piper nigrum fruits grown in Bangladesh, *World Journal of Pharmaceutical Sciences*, 2018, 2(9), 931-941, https://www.researchgate.net/ publication/329705936_Antioxidant_capacity_of_piper_longum_and_piper_nigrum_fruits_grown_in_Bangladesh.
83. Sutapa Das, Ratna Datta, and Subhangkar Nandy, Phytochemical screening and evaluation of anti-inflamatory activity of methanolic extract of *Abroma augusta* Linn., *Asian Pacific Journal of Tropical Diseases*, 2012, 2(1), S114-S117.
84. Esha Singla *et al*., Gallic acid protects against the COPD-linked lung inflammation and emphysema in mice, *Inflamm Res*, 2020, 69(4), 423-434, doi: 10.1007/s00011-020-01333-1. https://pubmed.ncbi.nlm.nih.gov/32144443/.
85. Sneha Choubey, Lesley Rachel Varughese, Vinod Kumar and Vikas Beniwal, Medicinal importance of gallic acid and its ester derivatives: a patent review, *PHARMACEUTICAL PATENT ANALYST*, 2015, 4(4), https://doi.org/10.4155/ppa.15.14, https://www.future-science.com/doi/abs/ 10.4155/ppa.15.14?journal Code=ppa
86. Michael N Clifford, Justin JJ van der Hooft, Alan Crozier, Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols, The *American Journal of Clinical Nutrition*, 2013, 98(6), 1619S–1630S, https://doi.org/ 10.3945/ajcn.113.058958, https://academic. oup.com/ ajcn/article/98/6/1619S/4577445.
87. Duangjai Tungmunnithum, *et al*., Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview, *Medicines (Basel)*, 2018 Sep; 5(3), 93, Published online 2018 Aug 25, doi: 10.3390/medicines5030093, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6165118/#__ffn_sectitle.
88. Jelenaa Ceramic, *et al*., The Oxygen Consumption Kinetics of Commercial Oenological Tannins in Model Wine Solution and Chianti Red Wine, *Molecules*, 2020 March, 25(5), 1215, https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC7179462/.
89. C Nepka, *et al*., Tannins, xenobiotic metabolism and cancer chemoprevention in experimental animals, *Eur J Drug Metab Pharmacokinet*, 1999, 24(2), 183-189, https://pubmed.ncbi.nlm.nih.gov/10510748/.
90. Minsu Jang, Yea-In Park, Yeo-Eun Cha, Rackhyun Park, Sim Namkoong, Jin I Lee, and Junsoo Park, Tea Polyphenols EGCG and Theaflavin Inhibit the Activity of SARS-CoV-2 3CL-Protease *In Vitro*, *Evidence Based Complementary and alternative Medicine*, 2020 Sep, Article ID 5630838, https://doi.org/10.1155/2020/5630838, https://www.hindawi.com/journals/ecam/2020/5630838/.
91. Suručić R, Tubić B, Stojiljković MP, *et al*., Computational study of pomegranate peel extract polyphenols as potential inhibitors of SARS-CoV-2 virus internalization, *Mol Cell Biochem*, 2020, https://doi.org/10.1007/s11010-020-03981-7, https://link.springer.com/article/10.1007/s11010-020-03981-7.
92. Mohammad Hojjati, Hassan Barzegar, Chemical composition and biological activities of lemon (*Citrus limon*) leaf essential oil, *Nutrition and Food Sciences Research*, 2017, 4(4), 15-24.
93. Khitma A. Sir Elkhatim, Randa A A Elagib, and Amro B Hassan, Content of phenolic compounds and vitamin C and antioxidant activity in wasted parts of Sudanese citrus fruits, *Food Sci Nutr*, 2018, 6(5), 1214–1219, Jul.https://www.ncbi.nlm.nih.gov/ pmc/articles/PMC6060895/#!po=2.72727.

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