Review Of Physiological Mechanisms Underlying The Use Of Garcinia Kola In The Treatment Of Asthma

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Abstract

Historically, plants have provided a source of inspiration for novel drug compounds, as plant derived medicines have made large contributions to human health and well-being. Their role is two ways in the development of new drugs: (1) they may become the basis for the development of new medicine i.e. a natural blueprint for the development of new drugs, or (2) a phytomedicine to be used for the treatment of disease. Though there is availability of various orthodox drugs for the treatment of respiratory track diseases in Nigeria, there is increase in the search for herbal remedies. The seeds of Garcinia kola (GK) forms a major part of the herbal preparation used in traditional African medicine practice for the treatment of various respiratory tract diseases including asthma. Because of the importance of GK as a herb commonly used in herbal medicine for the treatment of asthma, it becomes necessary to find out the physiological mechanism(s) underlying its use. This paper reviews the function(s) of its phytochemical contents and how they are beneficial in the treatment of asthma. Our review showed that xanthone and flavonoid which are its major phytochemical contents inhibit calcium influx and histamine release stimulated by IgE dependent ligands respectively. In conclusion, Garcinia kola appears to be very promising in the treatment and management of asthma.

BACKGROUND

Historically, plants have provided a source of inspiration for novel drug compounds, as plant derived medicines have made large contributions to human health and well-being. Their role is two ways in the development of new drugs: (1) they may become the basis for the development of new medicine i.e. a natural blueprint for the development of new drugs, or (2) a phytomedicine to be used for the treatment of disease. Though there is availability of various orthodox drugs for the treatment of respiratory track diseases in Nigeria, there is increase in the search for herbal remedies (1). The seeds of Garcinia kola (GK) forms a major part of the herbal preparation used in traditional African medicine practice for the treatment of various respiratory tract diseases including asthma.

Garcinia kola belongs to the family Guittiferae and it is commonly called “Orogbo” in Yoruba language while the English name is bitter kola. In Nigeria, the plant is valued because of its edible nut. The plant exhibits very potent pharmacological activities such as antioxidant, antibacterial antiviral, antifungal and anti-inflammatory properties (2,3,4,5,6,7). The anti-oxidant property of GK is attributed to its very high content of ascorbic acid (8). Phytochemistry of Gk have shown its content to include benxophenones, xanthones, biflavonoids, alkaloids, phenols, tannins and saponins (8,9,10,11,12,13,14,15).

Asthma is characterized by episodic or chronic wheezing, cough, and feeling of tightness in the chest as a result of bronchoconstriction (16). The fundamental cause is still unknown despite intensive research. However, three abnormalities are present: airway obstruction that is at least partially reversible, airway inflammation, and airway hyperresponsiveness to a variety of stimuli. A link to allergy has long been recognized, and plasma IgE levels are often elevated (17).

Because of the importance of GK as a herb commonly used in herbal medicine for the treatment of asthma, it becomes necessary to determine the physiological mechanism(s) underlying its use. This paper reviews the function(s) of its phytochemical contents and how they are beneficial in the treatment of asthma.

GARCINIA KOLA

Garcinia kola Heckel (Guttiferare, Bitter kola) is popular in southern Nigeria. The plant is extensively used in herbal medicine and as food. It is usually found in the tropical rain forest region of West Africa. It prevails as a multi-purpose tree crop in the home gardens of southern Nigeria (18). The tree is usually cultivated within villages in southern Nigeria. It grows to a height of about 12 – 14m and produces reddish, yellowish or orange coloured fruit (8,19). Each fruit contains 2 to 4 yellow seeds and a sour tasting pulp. The seeds when chewed have a bitter astringent taste. The flowering of the plant occurs between December and January while the fruits mature between June and August.

Garcinia kola is highly valued because of its medicinal use (20,21). The seeds are chewed as an aphrodisiac or used to cure cough, dysentery, chest colds in herbal medicine (22). This plant has been referred to as a "wonder plant" because every part of it has been found to be of medicinal importance (23). Garcinia kola could serve as a raw material for pharmaceutical industries (24). Gk is used in folklore remedies for the treatment of ailment such as liver disorders, hepatitis, diarrhea, laryngitis, bronchitis and gonorrhoea (7,25). The seed is used to prevent and relieve colic; can as well be used to treat headache (26). The plant has also found usefulness in the treatment of stomach ache and gastritis (27). Iwu (7) reported the use of this plant for the treatment of jaundice, high fever, and as purgative. Administration of GK seed extract caused an increase in testosterone production in Sprague–Dawley rates which is thought to be due to its antioxidant properties (28,29). Also, Adesanya et al., (19) confirmed the spermatogenic and tissue enhancing effect of GK extract in male Wistar rats. David et al., (30) showed that GK extract exhibits a dilatory effect on the alveolar ducts, alveolar sacs and alveoli thereby improves respiratory activities which may be due to its antioxidant properties in Swiss albino mice. Gk has been shown to inhibit smooth muscle activity. It relaxes the smooth muscles of the uterus and the intestine (31). Although, GK lacks caffeine (32), its alkaloid and biflavonoids fractions are said to relax the smooth muscles (31). Gk has a bronchodilatory effect (33,34).

ASTHMA

Asthma is a very common chronic disease involving the respiration system. There are three are basic abnormalities in asthma which are: (1) airway obstruction; that is at least partially reversible (2) airway inflammation (3) airway hyperresponsiveness to a variety of stimuli. Public attention in the developed world has recently focused on asthma because of its rapidly increasing prevalence, affecting up to one in four urban children (35). Asthma is caused by a complex interaction of environmental and genetic factors that researchers do not yet fully understand (36).

Environmental tobacco smoke, especially maternal cigarette smoking, is associated with high risk of asthma prevalence and asthma morbidity, wheeze, and respiratory infections (37). Poor air quality from traffic pollution or high ozone levels has been repeatedly associated with increased asthma morbidity and has a suggested association with asthma development and needs further research (37). Caesarean sections have been associated with asthma when compared with vaginal birth; a Meta–analysis found a 20% increase in asthma prevalence in children delivered by cesarean section compared to those who were not. It was observed that this is due to modified bacterial exposure during cesarean section compared with vaginal birth, which modifies the immune system (38). There is growing evidence that stress may influence asthma and other disease by influencing the immune system (37). Antibiotic use early in life has been linked to development of asthma in several examples; it is thought that antibiotics make one susceptible to development of asthma because they modify gut flora, and thus the immune system (39).

Over 100 genes have been associated with asthma in at least one genetic association study (40). However, such studies must be repeated to ensure that the findings are not due to chance. Many of these genes are related to the immune system or to modulating inflammation. Moreover, even among this list of highly replicated genes associated with asthma, the results have not been consistent among all of the populations that have been tested (40). This indicates that these genes are not associated with asthma under every condition, and that researchers need to do further investigation to figure out the complex interactions that cause asthma. Research suggests that some genetic variants may only cause asthma when they are combined with specific environmental exposures and otherwise may not be risk factors for asthma (36).

The fundamental problem in asthma appears to be immunological. In immunologic model, asthma is a disease mediated by reaginic (IgE) antibodies bound to mast cells in the airway mucosa. On reexposure to an antigen, antigen–antibody interaction on the surface of mast cells triggers both the release of mediators stored in the cells granules and the synthesis and release of other mediators

(16). The agents responsible for the early reaction mediating bronchoconstriction including histamine, tryptase and other neural proteases, leukotrienes C4 and D4, and prostaglandin causes muscle contraction and vascular leakage (16). Cytokines produced by TH_2 lymphocytes, especially GM–CSF and interleukins 4, 5, 9 and 13 which attract the active eosinophils and stimulate IgE production by B lymphocytes are thought to be responsible for more sustained bronchoconstriction, cellular infiltration of the airway mucosa and mucus hypersecretion of the late asthmatic reaction (41). These chronic inflammatory disorders of the airways that lead to tissue injury and subsequent structural changes are collectively called airway remodeling (42). TH_1 T cells make interferone-y, lymphotoxin, and IL-2. TH_1 and TH_2 cells differentiate unto polarized population from a common precursor. After development, they are believed to inhibit development of other cell types. TH_1 cells pay a dominant role in controlling intracellular pathogens like tuberculosis, while TH_2 cells play a dominant role in controlling extracellular pathogens like parasites and mites, and allergens like dusts and pollens (43). The absence of either of these population leads to enhanced immunopathology, even in conditions classically thought to depend on the other cell types.

Airway remodeling include 1) an increase in overall wall thickness, 2) an increase in airway fibrosis, 3) increase in smooth muscle mass, 4) abnormality in composition of the extracellular matrix and 5) an increase in vascularity (42). These changes have attracted interest due to the increased realization that these changes may account for aspects of asthmatic physiology that are poorly addressed with current anti–inflammatory strategies (44). A few studies have addressed the issue of response of putative remodeling mediators to therapy. IGF–□ appears to be resistant to steroid therapy, whether there is a reduction in measures of airway remodeling or not (45,46). Despite the suggestion that airway remodeling explains the lack of response to therapy of some patients, no study has specifically shown that those patient who either fail to respond to therapy or progress despite therapy do in fact show airway remodeling that fails to respond or progresses despite a reduction in inflammation (47). This observation could be due to disease heterogeneity. If this hypothesis was true, it would ultimately be necessary to characterize the pathological basis of each patients physiology before determining which therapy would be most beneficial in reversing or preventing airway remodeling in that individual patient (47).

The mechanisms underlying bronchial reactivity, such as ozone exposure, allergen inhalation, and infection with respiratory viruses also cause airway inflammation. In humans, the increase in bronchial reactivity induced by ozone is associated with an increase in the number of polymorphonuclear leukocytes found in fluid obtained by bronchial lavage or from bronchial mucosa biopsies. The increase in reactivity due to allergen inhalation is associated with an increase in both eosinophils and polymorphonuclear leukocytes in bronchial lavage fluid. Whatever the mechanisms responsible for bronchial hyperreactivity, bronchoconstriction itself seems to result not simply from the direct effect of the released mediators but also from their activation of neural or humoral pathways.

ACTIONS OF XANTHONES

Xanthone have anti-asthmatic activity by dependently inhibiting the Ca^{2+} influx induced by either noreprinephrine or high K+, suggesting that xanthone might act as a blocker of both receptor–operated and voltage–dependent Ca^{2+} channels (6). Furthermore, xanthone causes increase in the level of intracellular cyclic adenosine $3^{'}$, $5^{'}$–monophosphate (cAMP) but not cyclic guanosine $3^{'}$, $5^{'}$–monophosphate (cGMP) content (6). Chairungsrilerd et al. (21) reported that xanthone showed inhibitory effects on cAMP phosphodiesterase. Intracellular levels of cAMP can be increased by □-adrenoceptor agonist, which increase the rate of its synthesis by adenyl cyclase (AC) or by phosphodiesterase (PDE) inhibitors such as xanthone, which slow the rate of its degradation.

ACTION OF FLAVONOIDS

Flavonoids have anti–asthmatic activity by inhibiting platelet-activating factor (PAF), phospholipase A_2 (PLA_2) and phosphodiesterase (PDE) (48,49). Flavonoids protect against allergies, inflammation, free radicals and platelet aggregation (50,51,52,53). These observations support the importance of Gk in traditional medicine for the treatment of various conditions.

Flavonoids have been shown to exhibit a predilection to inhibit histamine release stimulated by IgE-dependent ligands (54). Copper a transitional metal; most effectively block the inhibitory activity of flavonoids, possibly through a chelation mechanism (55). Zinc deficiencies can lead to excess copper levels, since zinc and copper compete for absorption. Also, a high intake of vitamin C and zinc decrease the absorption of copper. Intake of Gk will therefore reduce the inhibition of antihistamine activity of

flavonoids by copper which is as a result of its high content of vitamin C and zinc. Middleton and Drzewiecki (56) noted that naturally occurring plant flavonoids affect a variety of cell activation phenomena including the secretion of histamine from human basophils. They also showed that flavonoids inhibit the degranulation of mast cells. Degranulation of mast cells would release not only histamine, but all the mediators of the allergy response.

Simoes (57) reported that flavonoids exhibited anti–spasmodic and anti–inflammatory properties induced by acetylcholine, histamine, noradrenaline and barium chloride in four different smooth muscles. In addition, flavonoids inhibit antigen-induced release of histamine from mast cells, basophils and also inhibit contractions induced by histamine, acetylcholine and PGE¬¬¬$_2$. It was noted that this effect was concentration dependent.

Flavonoids inhibit phospholipids metabolism and 5-lipoxygenase (5–LO). Leukotrienes are derived from arachidonic acid through 5–LO and the nucleophilic attack to produce peptidoleukotrienes. These 5–LO products mediate constriction of airway smooth muscles, leukocyte chemotaxis (58,59) and vascular permeability (58,60). Therefore inhibiting 5–LO can attenuate leukotriene production.

The presence of phenol in GK further indicated that it could act as anti-inflammatory, antioxidant and immune enhancers (61). Phenols have been responsible in having the ability to block specific enzymes that cause inflammation. They also modify the prostaglandin pathways and thereby protect platelet from clumping (8).

FINDINGS / CONCLUSION

From this review, the following could be the underlying physiological mechanisms by which Garcinia kola may be beneficial in the treatment of asthma:

- Inhibition of Ca2+ influx by acting as a blocker of both receptor-operated and voltage–dependent Ca2+ channels
- Increasing the intracellular levels of cAMP by inhibiting the effects of phosphodiesterase
- Inhibition of histamine release stimulated by IgE dependent ligands
- Inhibition of platelet–activating factor and platelet aggregation
- Its high vitamin C and zinc content
- Inhibition of 5-lipoxygenase (5-LO) pathway thereby attenuating leukotriene production.

In conclusion, Garcinia kola appears to be very promising in the treatment and management of asthma. There is therefore the need to further examine its various phytochemical contents on respiratory smooth muscle, with a view to possibly formulating its extracts or active constituents as medicines.

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