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Original Research Article

Drug-Phytochemical Interaction: *In vitro* Investigation of the Effects of *Aframomum melegueta* Seed Extract on Acetaminophen and Amlodipine Absorption

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ABSTRACT

The concomitant use of herbal preparations by patients presenting in health facilities may impact the pharmacokinetic processes of orthodox drugs. This study was aimed at evaluating the impact of phytochemicals of *Aframomum melegueta* (AM) seeds on the bioavailability of acetaminophen (N-acetyl-p-aminophenol) and amlodipine. The *everted intestinal sac model* was used to assess the transfer of Acetaminophen and amlodipine across the intestinal wall. A portion of the small intestine was excised, everted, filled with Tyrode solution with both ends ligated to make a closed loop, and immersed in a beaker containing a concentration of the test drug either alone or in the presence of AM seed extract (AMSE). After a time to achieve transfer equilibrium, the everted tissues were removed, and the concentration of the test drug was determined in these serosal fluids to assess transfer efficiency. The study showed that AM seed extract severely inhibited the intestinal transfer of acetaminophen by as much as 82.4% while amlodipine transfer was enhanced by up to 94.5%. Serosal concentrations of acetaminophen in the absence and presence of AMSE were 7.62 ± 0.95 µg ml^{-1} and 1.34 ± 0.96 µg ml^{-1} (P<0.001), respectively while that for amlodipine were 2.54 ±1.03 µg ml^{-1} and 4.94 ± 0.739 µg ml^{-1} respectively. The depression of APAP transfer was suggested to be due to chemical interaction with nitric oxide produced by the interaction of the phytoestrogens in the extract on the GPCR-bound estrogen receptor. This type of interaction may have serious health consequences.

Keywords: Acetaminophen, Intestinal transfer, Nitric oxide, *Aframomum melegueta*, Phytochemicals

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Introduction

The concurrent use of complementary and herbal preparations by patients in health facilities is of major concern for treating diseases effectively and managing health challenges. Drug-herb interaction is a common phenomenon that is underrated because of the widely held belief that herbs are generally safe and free of any adverse health consequences. This is a major basis for classifying herbal preparations as food supplements, even by regulatory authorities saddled with the responsibility of safeguarding the health and well-being of the general populace. These interactions have been severally studied, and in most cases, the focus is usually on the possible pharmacodynamic augmentation or antagonism of orthodox medications and the tendency of herbal preparations to interfere with the pharmacokinetic properties of these medications.[1,2] A good number of these interactions have been reported.[3,4]

Aframomum melegueta (AM) seeds are important components of many herbal/complementary preparations that have been shown to possess varied biological effects[5,6,7,8] including the ability to interfere with drug concentration assays in biological fluids[9].

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The methanolic extract of *Aframomum melegueta* seeds (AMSE) have been reported to reduce both systolic (SBP) and diastolic (DBP) blood pressures in normal and hypertensive subjects,[10] and abolish castor oil-induced diarrhea in rodents,[11] with both effects attributed to possible direct interaction of the components of these seeds to induce smooth muscle relaxation in both the vascular and gastrointestinal tissues respectively.

Arising from the above, we hypothesized that relaxation of the gastrointestinal (GIT) wall may have consequences on the bioavailability of orally administered drugs depending on where in the GIT length the drug is being absorbed from, may delay or enhance the rate of drug absorption. To test this hypothesis, we carried out a study on the effect of prior oral administration of AMSE on the pharmacokinetics of orally administered acetaminophen (N-acetyl-p-aminophenol; APAP) in rodents and, to our surprise, 30 min prior oral administration of AMSE to the rats severely reduced the total AUC of APAP by as much as 83%.[12]

This study aimed to further explore the observed AMSE effect on APAP bioavailability by carrying out gastrointestinal transfer studies of APAP and another drug, amlodipine (AML) using the *everted intestinal sac* method,[13] precluding the influence of the metabolizing liver enzymes on drug absorption. The everted intestinal sac model is used to evaluate intestinal absorption characteristics of active principles. APAP was included in this study due to its ubiquitous over-the-counter use in mild pain, headache relief, fever reduction, and as a major ingredient in many cold medications (obvious reasons) while the inclusion of AML, a dihydropyridine calcium channel blocker was because of its primary biological activity for the management of blood pressure; an activity that corresponds with the blood pressure-lowering effect of AMSE albeit with a known mechanism of action. Also, AML is a widely and chronically prescribed antihypertensive drug which also makes it liable to concurrent use with herbal preparations. Therefore, it is necessary to explore the impacts of herbal preparations on orthodox drugs when taking concurrently as they may have consequences on their biological action and clinical use.

Materials and Methods

Equipment
Absorbance measurements in this study were made with Spectrovis® Plus spectrophotometer (range: 380-950 nm; resolution: ~2.5 nm optical resolution, 570 wavelengths, 1 nm reporting intervals), with Logger Pro ® Software (Vernier International, 5026 Calle Minorga, Sarasota, FL 34242 U.S.A.) running on an Intel Pentium® PC.

Drugs, Chemicals, and Reagents
Acetaminophen (N-acetyl-p-aminophenol; APAP), Trichloroacetic acid (TCA), concentrated hydrochloric acid, sodium nitrite, sulphamic acid, sodium hydroxide, methanol, heparin, and thiopental sodium were analytical grade reagents sourced from Sigma Chemical Company (Sigma-Aldrich Laborchemikalien GmbH. D-30926, Seelze, Germany); Amlodipine besylate tablets were purchased from Pfizer ™ Inc., 66 Hudson Boulevard East New York, USA.

Preparation of Reagents
15% trichloroacetic acid, sodium nitrite, and sulphamic acid were prepared by dissolving 15 g of each substance in 100 mL of distilled water, respectively. Heparinized saline was prepared by mixing 1 mL of heparin with 50 mL of normal saline.

Preparation of Plant Extract
Dried *A. melegueta* fruits were bought in June 2019 from a local market in Abia State, Nigeria, authenticated by a match against the University of Uyo Botanical Gardens Herbarium Species Collection; Voucher No: MIA2011, and further dried to a consistent weight in a 40ºC oven. The pods were opened to release the seeds which were ground into fine powder using a laboratory manual grinder. 100g of the powder was weighed and extracted in a Soxhlet Extractor of 500 mL capacity. The material was sequentially extracted with petroleum ether followed by methanol. The methanol extract was evaporated to dryness at a reduced temperature of 40^0C and stored in a desiccator until further use. The percent yield of the methanol extract was calculated to be 6.7%.

Preparation of Everted Intestinal Sacs
The everted intestinal sacs were prepared according to the method described by Tactacan *et al*.[13] In brief, after a twelve-hour fast, rats weighing 150-170 g were anaesthetized and their small intestines were removed quickly. The small intestines were cut into smaller pieces about 6-7 cm, flushed with Tyrode solution to remove debris and everted using a strip of thin wire. The everted sacs were subsequently weighed and ligated at one end, 0.5 mL of Tyrode solution was introduced into the resulting pocket and the sac was then further ligated at the other end. The Tyrode-filled everted intestinal sacs were weighed again and then dropped into appropriate experimental drug solutions for the *in-vitro* drug absorption study.

In Vitro Intestinal Absorption of AML and APAP in the Presence and Absence of AMSE
Tyrode-filled everted intestinal sacs as prepared above were dropped into 500 mL beakers containing either the test drug solution (AML or APAP; 100 µg ml^{-1}) alone or test drug solution in the presence of 50 µg ml^{-1} AMSE and the time noted. At time intervals of 5, 10, 15, 20, 25, 30, 60, and 90 minutes the intestinal sacs were taken out of the incubation medium, damped dry and re-weighed. The contents from the serosal side of the sacs were drained into plain sample bottles labeled following the time of sampling. The contents in the sample bottles were assayed for the test drug using the appropriate assay methods with modifications for sample volume.

Assay of APAP and AML in serosal fluids
In brief, the fluid in the serosal sac after incubation was emptied into microcentrifuge tube containing 0.1 mL trichloroacetic acid, vortex-mixed and centrifuged for five minutes. Subsequent manipulation of the sample proceeded as follows according to the drug being assayed;
Amlodipine: the method of Doijad *et al.*[14] was used with modifications. 0.3 mL of the clear supernatant was decanted into plain sample bottles. To these, 0.3 mL of $FeCl_3$ was added followed by another 0.3 mL of potassium ferricyanide. The contents in the bottles were left to stand for ten minutes for the reaction to complete. Afterwards, the final volume in the sample bottles were made up to 3.0 mL with distilled water. The absorbances of the samples were read at 393.1 nm, against reagent blank of water. AML concentrations were obtained from the standard curve of AML earlier constructed.
Acetaminophen: the method of Glynn and Kendal[15] as reported by Shihana *et al.*[16] was employed. 0.1 mL of the clear supernatant was placed into plain sample bottles containing 0.1 mL hydrochloric acid and 0.1 mL of 15 % sodium nitrite. The solution was left to stand for two minutes and afterwards 0.2 mL of 15 % sulphamic acid was added, followed by 0.5 mL of 15 % sodium hydroxide. The absorbance of the samples was read at 430.2 nm against reagent blank. Acetaminophen concentrations were determined from the standard curve constructed earlier.

Statistical analysis
Parameter values were recorded as Mean ± SEM and comparison of mean values of relevant parameters were made using the two-tailed Student's *t-test* statistics. Significance was accepted at the 0.05 level of probability ($P<0.05$). All statistical tests were carried out using the GraphPad Prism (GraphPad Prism Five for Windows, version 5.01. GraphPad Software Inc.)

Results and Discussion

Figure 1A and 1B shows the pattern of serosal drug concentrations of AML and APAP both in the absence and presence of AMSE. The concentration of APAP reaching the serosal side of the everted intestinal sac was found to be rapid within the first 10 minutes, slowed down up to 30 minutes, and gradually increased to a mean value of 11.4 ± 1.72 µg ml^{-1} in 90 minutes. In the presence of AMSE, the maximum concentration reached was 4.67 ± 0.995 µg ml^{-1} ($P<0.05$) showing that acetaminophen absorption in the presence of AMSE was significantly reduced. In contrast to APAP alone, the maximum concentration of AML was reached within 25 min and 30 min. AMSE resulted in an enhancement of AML transfer which was particularly significant around the time of peak transfer. Peak concentrations of AML in the absence and presence of AMSE were 4.16 ± 0.43 µg ml^{-1} and 9.00 ± 1.55 µg ml^{-1} respectively ($P<0.05$). Table 1 shows the aggregate values of the serosal concentrations of the two drugs calculated across all time points by performing the analysis of variance between the serosal concentration of the drug with or without the presence of AMSE. The results showed. that the post-incubation serosal concentration of AML was 2.54 ± 1.03 µg ml^{-1} and 4.94 ± 0.74 µg ml^{-1} in the absence and presence of AMSE respectively while for APAP, the values are 7.62 ± 0.95 µg ml^{-1} and 1.34 ± 0.96 µg ml^{-1} respectively ($P<0.001$).
Post-incubation weights of intestinal tissues following incubation in APAP solution without and with AMSE were slightly increased although the increases were minimal: (APAP, 0.0604 ± 0.0184 g); (APAP+AMSE, 0.0738 ± 0.0376 g). In contrast, there was a reduction in tissue weight recorded for AML in the absence (0.110 ± 0.0198 g) and presence (0.0739±0.0188 g) of AMSE. Although the weight change for both drugs followed different trajectories, there was no significant difference between the changes in tissue weight with or without the presence of AMSE.
In the presence of AMSE, there was a significant reduction in the transfer of APAP from the mucosal to the serosal media, constituting 82.4% of the starting mucosal concentration on average (Figure 1A). Interestingly, this value is similar to the 83% reduction we observed in our *in-vivo* study on AMSE effect on APAP bioavailability in rodents.[12] In contrast, however, AMSE enhanced the mean concentration of AML crossing the intestinal wall up to 94.5% of the starting mucosal level (Figure 1B). While the improvement in AML transfer across the GIT corroborated our expectations and hypothesis; that of APAP was

baffling; it suggested that this phenomenon could not have been a general phenomenon in the absorption process but was somehow peculiar to APAP itself. It was observed that the reduced bioavailability of APAP in the presence of AMSE has little or nothing to do with its alteration of APAP metabolism on its first transit to the circulation through the liver; the well-known "first pass" effect. This does not however negate the possibility of AMSE influencing the metabolic disposition of APAP in the intestinal tissue itself.

During the study, we did observe that the everted intestinal tissues were more relaxed, flabby, and elongated after incubation in the presence of AMSE. Though we did not measure the degree of relaxation, this is most probably caused by the phytochemicals in AMSE and may also explain the increased transfer of AML and an enhanced serosal concentration (94.5%) that was recorded; almost twice as much as that without AMSE. Why this same relaxation did not enhance the APAP transfer across the GIT tissue may depend on the nature of the relaxation itself and the impact this has on APAP, and the most likely reason is the possible interaction between APAP and the components of AMSE that made it impossible for the drug to transit into the serosal compartment. This interaction may be because of the physical and chemical characteristics of APAP.

Table 1: Serosal drug concentrations in the absence and presence of AMSE

Drug	Serosal drug concentration (µg ml^{-1}) †	Serosal drug concentration + AMSE (µg ml^{-1})	T-Test
APAP	7.62 ± 0.95	1.34 ± 0.96	0.0003***
AML	2.54 ±1.03	4.94 ±0.739	0.1304
	(n = 32)	(n = 32)	

In vitro studies on drug absorption was carried out using everted intestinal sac. Data are presented as Mean + SEM). † Serosal drug concentration represents the average value of all the drug concentrations recorded for all time points as determined after ANOVA. *** P<0.001. n = 32.

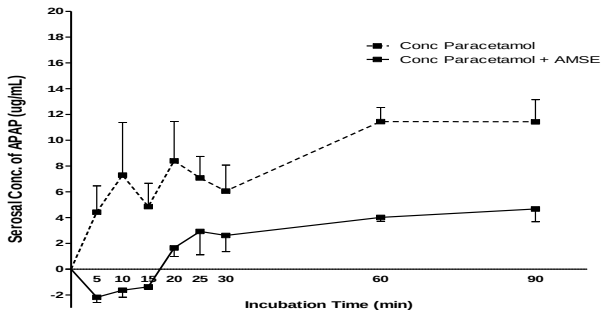

Figure 1A: Serosal acetaminophen concentration alone and in the presence of AMSE.

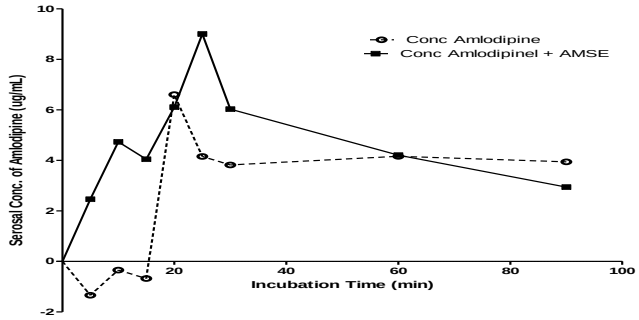

Figure 1B: Serosal concentration of amlodipine alone and in the presence of AMSE.

The study also revealed that the post-incubation tissue weight of the *everted intestinal sacs* was slightly increased in the tissues used for APAP and AML assays (Table 2; Figure 2A and 2B), although in the absence of AMSE, the post-incubation tissue weight was lower than the starting weight of the tissues in the AML tests; a situation that can be explained by the possible loss of tissue fluid due to the tonicity of the extracellular and intracellular drug solutions. In the presence of AMSE, this loss in tissue weight was slightly reversed but not to the extent of totally counteracting the effect of the incubation in AMSE. When compared to the tissue weight-change in APAP, it was found that even in the absence of AMSE, APAP was able to cause a slight weight increase in the post-incubation tissue compared to the pre-incubation weight of the tissues; a situation slightly enhanced by the presence of AMSE. It does suggest that APAP may either not have enough tonicity in solution as to influence fluid movement from the tissue or that whatever component was interacting with APAP was doing so either in the extracellular mucosal compartment or within the intestinal tissue itself.

In an earlier review of interactions between APAP and phytotherapies,[17] the authors conducted an extensive database search of relevant publications on the subject matter. The outcome revealed two major points: (i) the effect of phytotherapies on phase one metabolism of APAP with its hepatotoxic action and, (ii) effects on its analgesic and antipyretic action; there was however no report on the transfer function of the GIT in the absorption process of APAP bioavailability. The improvement of the post-incubation weight change brought about by AMSE in both APAP and AML preparations in this study did suggest a direct involvement of AMSE in tissue function and physiology. The implication of this on the depression of APAP absorption requires further enquiry and elucidation.

Aframomum melegueta (Rose) K. *Schum* is a spice plant renowned for its medicinal properties, and its seeds are extensively used in herbal preparations.[10] It is also known to contain various phytochemicals such as phenols, diterpenoids, sesquiterpenoids, and flavonoids which are very well documented and reported to be very bioactive.[18] Another important chemical class found in the plants of this genus is the arylalkanoids.[19] They contain a benzene ring most usually attached to linear alkyl chain of varying length, but of particular interest are the little-known diarylheptanoids; groups of compounds that bear two aryl groups at both ends of a seven-carbon linear chain (the 1,7-diphenylheptane skeletons). They were isolated for the first time from the seeds of *Aframomum letestuianum*.[20] The arylalkanoids have been reported to possess ability to interact with the estrogen receptors [21] and are referred to as phytoestrogens. These particular group of chemicals may be responsible for reduced APAP intestinal transfer.

Estrogens are endogenous hormones produced in the body that are best known for their transcriptional modulation activities. They act on nuclear hormone receptors ERα and ERβ to modulate the transcription of various genes responsible for the synthesis of varieties of metabolic and regulatory proteins. In addition to these well-documented actions, they are also known to produce acute effects in the body that are outside their known nuclear transcriptional functions. These acute effects are mediated by another set of membrane-bound G-protein-coupled receptors (GPCR), which are linked to soluble enzymes guanylate and adenylate cyclases responsible for the production of cGMP and cAMP respectively, and ultimately to nitric oxide (NO) synthesis through nitric oxide synthase (NOS) in the endothelial cells of blood vessels. Al-Shboul *et al*. also showed that oestrogen relaxed gastric smooth muscle cells through NO and cGMP-dependent mechanisms mediated through oestrogen receptors (ERs) α and β.[22] The major actions of NO include the dilation of blood vessels and a protective role against endothelial dysfunction.[23] It appears reasonable to suggest that the phytoestrogens in the seeds of AM acted on oestrogen receptors: GPCRs of membrane-bound estrogen receptors, ERα, and ERβ to induce the production of copious amounts of NO in the smooth muscle tissues as well as in the endothelial cells leading to the relaxation of these tissues. This will explain the relaxant effect of the AMSE on the GIT tissues, as well as its decrease of blood pressure,[10] and the protective effect exhibited by oestrogen on endothelial function and other predisposing risk factors for coronary artery disease (CAD).

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Table 2: Change in tissue weight following *in vitro* drug incubation in the absence and presence of AMSE in everted sac absorption model

Drug	Δ Tissue weight after drug incubation† (g)	Δ Tissue weight after drug + AM incubation† (g)	T-Test
APAP	0.0604 ± 0.0184	0.0738 ± 0.0376	0.5054
AML	0.110 ± 0.0198	0.0739 ± 0.0188	0.2786
	(n = 32)	(n = 32)	

In vitro studies on drug absorption were carried out using everted intestinal sac. Data are presented as Mean ± SEM). Change in tissue weight represents the average value of all the everted tissue weight changes across all time points.

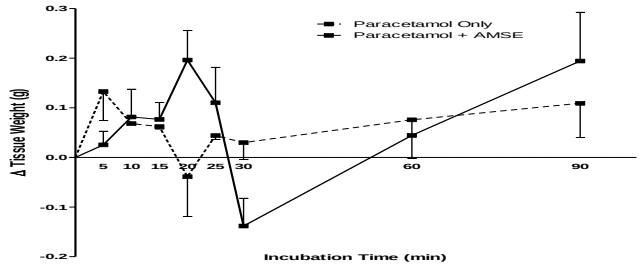

Figure 2A: Changes in tissue weight following incubation of everted sac in a solution of acetaminophen with or without AMSE

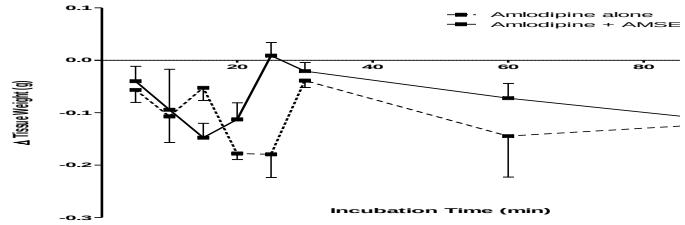

Figure 2B: Changes in tissue weight following incubation of everted sac in a solution of amlodipine with or without AMSE

Not too long ago, the NOS/NO coupled pathway was linked to the cyclooxygenases (COX-1 and COX-2) systems. These are enzymes responsible for the production of prostanoids, which are endogenous molecules produced in the body that mediate inflammatory responses as well as serve as important signal transducers in some vital tissue and organ functions. The major products of COX activity are prostaglandin E_2 (PGE_2), prostacyclin (PGI_2), and thromboxane (TxA_2). The activity of COX has also been shown to be dependent on NO molecule whereby NO interacts with the active center of COX to stimulate the production of prostanoids. APAP has been known to inhibit COX activity which was believed to be part of its mode of action as an analgesic drug. This inhibition is said to be differential on both the COX-1 and COX-2 enzymes such that APAP shifts the balance of action of prostanoids against prostacyclin production. Prostacyclin is the prostanoid that is responsible for vasodilation of vascular beds.[24] Inhibition of this coupled pathway in any way will therefore impact the inflammatory function, and it is this influence that is attributed to the ability of non-steroidal anti-inflammatory drugs (NSAID). While other NSAIDs are known to inhibit COX enzymes directly, APAP appears to influence the pathway in a unique manner which may partly explain its modest analgesic and anti-inflammatory effects.

APAP is an orally effective analgesic that is highly absorbed from the GIT and undergoes first-pass metabolism with peak plasma concentrations reached between 60-120 minutes. It distributes rapidly and evenly throughout most tissues and fluids,[25] and with this high presence in all tissues, inhibition of prostacyclin production and thereby unmodified vasoconstriction of the vascular bed by thromboxane will prove potentially dangerous to individuals taking APAP.[26] This scenario has already been reported severally in subjects prone to disruption of their NO status and examples are: (i) Healthy subjects at a single dose of 3g had their COX-catalyzed synthesis of prostacyclin (PGI_2)- a potent vasodilator and inhibitor of platelet aggregation-potently inhibited, and by contrast, the synthesis of thromboxane (TxA_2)-, a potent vasoconstrictor and platelet activator, was found not to be inhibited by paracetamol in the subjects.[24,26] (ii) Sudano and colleagues found that a 2-week administration of 1g APAP to coronary artery disease (CAD) patients resulted in small blood pressure increase in the patients.[27] (iii) A single oral dose of 500 mg paracetamol has also been shown to reduce urinary excretion rate of PGI_2 metabolite by maximally 60% which is an indication of reduced production of prostacyclin synthesis without a concomitant decrease in the metabolite of TXA_2.[28]

The unique characteristic of APAP is that it most probably utilizes a different mechanism in its effect on the coupled inflammatory pathway. APAP is very reactive towards NO and nitrites (NO_2). This reactivity does not require enzyme catalysis and it has also been achieved *in-vitro* by incubating a phosphate-buffered (pH 7.4) solution of sodium nitrite and APAP in liquid nitrogen (-196ºC) for a short time, which resulted in the formation of polymeric and nitrated APAP species.[29] Di-APAP and 3-nitro-APAP were among the reaction products obtained. The nitration reaction on the phenolic ring of APAP is so prominent that it has also been used as the basis for the determination and quantification of APAP.[30] This unique ability then explains why APAP could not cross the intestinal barrier in our study and why its bioavailability in *in vivo* studies have been very poor; profuse NO molecules produced by the interaction of the phytoestrogens in AMSE interacted with APAP to form nitrated and conjugated metabolites in the GIT tissues and because these type of interaction does not occur with AML, AMSE could not inhibit AML transfer and rather improves it slightly by relaxation of the GIT wall which modestly offered a wider surface area for AML absorption.

The cardiovascular consequences of these APAP/NO interactions have been reported in the literature and span a wide dosage range. Upon 3g APAP administration in four healthy subjects, a considerable and sustained decrease in prostacyclin production was observed [24] which is a consequence of depletion of NO and the inability to stimulate the COX-dependent synthesis of the inflammatory mediator. A single oral dose of 500 mg paracetamol has been shown to reduce urinary excretion rate of PGI_2 metabolite by maximally 60% which is an indication of inhibition of prostacyclin synthesis without a concomitant decrease in the metabolite of thromboxane.[28] Bippi and Frolich [31] had also earlier reported that administration of sub-clinical dose of 500 mg of APAP given alone and in combination with acetylsalicylic acid resulted in a significant decrease in the synthesis of prostacyclin.

It does appear however, that these effects of APAP on the COX system is mainly exerted on the constitutive isoform of NOS (cNOS) to which the endothelial variety belongs, and that the effect on inducible (iNOS) and neuronal (nNOS) isoforms are less manifest and depends on particular tissues and anatomical locations of such. In murine macrophages, APAP at pharmacologically relevant plasma concentrations (60–120 μM), has been reported not to affect iNOS activity.[32] At supra-pharmacological concentrations (2.5 and 10 mM), APAP has been reported to inhibit iNOS gene expression and iNOS activity in RAW 264.7 cell line macrophages;[33] by contrast, APAP (up to 10 mM) has been reported not to affect neuronal NOS (nNOS) and iNOS activity in rat cerebellum and HUVECs.[34] Others have reported that paracetamol (100 μM) did not affect nNOS activity in cerebellum but inhibited NOS activity in murine spinal cord slices as measured by the radiolabelled L-citrulline assay.[35]

Conjugated metabolites such as APAP-sulfate-APAP and APAP-S-S-APAP in addition to the classical APAP metabolites have all been demonstrated in mice [36] and there is nothing to preclude it from also occurring in humans. The fact that these metabolites of APAP can easily be produced *in vitro* at low temperatures shows how easy their formation is. The nitration of APAP by nitrous acid is so stable that it has formed a basis for the quantification of APAP in biological fluids.[16,30]

As shown by this study, APAP bioavailability can be severely impeded by phytoestrogens in herbal complementary preparations. Beyond this apparent inconvenient loss of analgesic effect of APAP, which *ab initio*, is a very modest, serious implication of this particular unique occurrence with phytoestrogens-common components in herbal medications-may have far-reaching consequences in populations using APAP in the presence of raised basal oestrogen levels, those with risk factors for CAD and diabetes or healthy individuals who are very likely to be on prolonged exposure to APAP.

Conclusion

This study has shown that the phytochemicals in *A. melegueta* seeds impeded the bioavailability of APAP by sequestrating it in the GIT tissue through possible chemical interactions between phytochemical-induced NO and APAP. Beyond the certain loss of modest APAP analgesic effect in patients, there are other underlying consequences to this type of interaction that may have profound consequences on public health. However, serious attention must be given to the possible concurrent intake of orthodox and complementary medications in other to avoid this type of potentially dangerous interaction. The ramifications of these peculiar APAP-phytoestrogen interactions are currently the subject of ongoing scrutiny.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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