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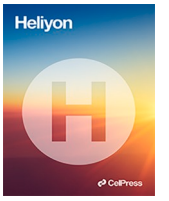

Review article

Meat tenderization using acetaminophen (paracetamol/APAP): A review on deductive biochemical mechanisms, toxicological implications and strategies for mitigation

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ABSTRACT

Meats consist of edible portions originating from domestic and wild animals. Meat's palatability and sensory accessibility largely depend on its tenderness to consumers. Although many factors influence meat tenderness, the cooking method cannot be neglected. Different chemical, mechanical, and natural means of meat tenderization have been considered healthy and safe for consumers. However, many households, food vendors, and bars in developing countries engage in the unhealthy use of acetaminophen (paracetamol/APAP) in meat tenderization due to the cost reduction it offers in the overall cooking process. Acetaminophen (paracetamol/APAP) is one of the most popular, relatively cheap, and ubiquitous over-the-counter drugs that induce serious toxicity challenges when misused. It is important to note that acetaminophen during cooking is hydrolyses into a toxic compound known as 4-aminophenol, which damages the liver and kidney and results in organ failure. Despite the reports on the increase in the use of acetaminophen for meat tenderizing in many web reports, there have not been any serious scientific publications on this subject. This study adopted classical/traditional methodology to review relevant literature retrieved from Scopus, PubMed, and ScienceDirect using relevant key terms (Acetaminophen, Toxicity, Meat tenderization, APAP, paracetamol, mechanisms) and Boolean operators (AND and OR). This paper provides in-depth information on the hazard and health implications of consuming acetaminophen tenderized meat via genetic and metabolic pathways deductions. Understanding these unsafe practices will promote awareness and mitigation strategies.

1. Background

Meat is the edible portion of domestic and wild animals [1]. It is rich in proteins, essential amino acids, and fats, including omega-3 fatty acids, minerals, vitamins, and folic acids [1–3]. However, these nutritional constituents and the sensory evaluations in meat varies due to different genotype, diet, meat cut, and climate and environmental conditions influence [4]. Due to the growing human population, meat consumption in developing countries will exponentially increase to satisfy human protein needs [5]. Healthy meat consumption is crucial in maintaining life and health status in human evolution. It provides essential protein requirements in humans

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[5–7]. Meat is ranked among the vital, nutritious, and calorie-rich natural products humans consume to cover their daily body needs for growth and development [1]. Although few studies have linked its consumption to the possible elevation of cardiovascular diseases, cancer, and metabolic disorders [8–10], its roles in the brain and intellectual advancement cannot be neglected [3]. A worrisome concern of the meat industries in many Africa nations such Nigeria, is the high tendency of meat contamination from the onset of the animal slaughter in the abattoir to the stage of final consumption by customers through sale by food vendors [11]. Hence, enforcement of handling/treatment precautionary measures at each stage of meat production may be the way forward. In many African nations, regulatory agencies for food safety have failed in enforcing food vendors to operate in such a manner that is generally regarded as safe and healthy for the consumers, probably due to deep-rooted corrupt practises [11,12]. This paper present one of the very common ill-practice by food vendors - using acetaminophen for meat tenderization.

Paracetamol (acetaminophen) is an antipyretic and analgesic drug available over the counter and is one of the most prescribed analgesic drugs globally [13]. It is the recommended first-line drug for pharmacological therapy by WHO and various international guidelines for managing acute and severe pain conditions using painkiller drugs [14,15]. It exists in different forms, such as capsules, liquids, tablets, and granules. It is used to manage mild to moderate pains and their severity. Some conditions treated with paracetamol include muscle, head, back, toothaches, colds, flu, fever, sore throat, and phycological processes [13–16]. Although the mechanism of acetaminophen analgesic action is largely unknown, studies have demonstrated that it inhibits prostaglandin synthesis within the central nervous system and the peripheral tissues [17]. Acetaminophen is administered orally and also intravenously. The recommended dose for adults and teenagers weighing at least 44.90 kg is 1000 mg at once but not above 4000 mg in 24 h. While children less than 12 years are advised not to take more than 5 doses in 24 h and strictly adhere to the number of mg per recommended dose for children with respect to their weight and age [18]. It has been reported that an overdose of this drug causes liver damage and possible death [13,17–19]. There may also be side effects or allergic reactions associated with consuming acetaminophen. These side effects may include breathing difficulty, rashes and redness of the skin, swelling of the face, and blisters on the tongue and lips. In severe cases, stomach pain, loss of appetite, weakness, dark urine, and jaundice are reported [13]. Notwithstanding the toxicity and side effects of acetaminophen consumption, many food vendors have, unethically daily, used this drug as a faster means of tenderizing meat [12].

Tenderization is a vital process employed in cooking to ensure improved palatability and sensory attributes of meat [20]. The major factors determining meat tenderness are collagen content, aging processes, muscle contraction during slaughter, sex, genetic influence, species, and stress conditions [3,21]. The cooking method is also a determinant of meat tenderness [22]. The enzymatic method of meat tenderization has been adjudged healthier and more economical than the conventional physical and chemical methods [20]. Proteinases from plants such as papain from papaya, bromelain from pineapple, and ficin from fig have effectively tenderized connective tissue and muscle proteins in meat [20,23]. The sensory attributes of meat are based on its visual appearance, palatability to the mouth, and the flavor produced [3]. The consumers' satisfaction and meat eating quality are principally determined by its tenderness and flavor [4]. It has been reported that many households, food vendors, and bars, especially those operated by low-income owners, apply the unhealthy use of paracetamol (acetaminophen) in meat tenderization due to the high cost of fuel procurements and precipitation of cooking time [12]. Unfortunately, acetaminophen, during cooking, hydrolyses into a toxic compound known as 4-aminophenol, which damages the liver and kidney and results in organ failure [12,19].

Many studies have focused mainly on the processes and methods of meat tenderization and the application of exogenous plant enzymes (proteases) for achieving meat tenderness [3,11,20,23]. There is a paucity of information on the unhealthy use of acetaminophen in meat tenderization and its possible health hazard to consumers. Therefore, this review focuses on this subject and recommends solutions to mitigating these dangerous practices by food vendors to pave the way for green and sustainable meat tenderization.

2. Methodology

This study adopted classical/traditional methodology to review relevant literature retrieved from Scopus, PubMed, and ScienceDirect databases using key terms such as Acetaminophen, Toxicity, Meat tenderization, APAP, paracetamol, and mechanisms. The Boolean operators (AND and OR) were used to streamline the search focus and retrieve relevant publications on this subject. The paper included in this review much be reported in the English language and be focused on acetaminophen and its toxicities as well as other alternative and safe methods for tenderizing meats and meat products. Recent studies were prioritized over older ones, especially in cases of information redundancy.

3. Chemistry of acetaminophen

Acetaminophen (*N*-(4-hydroxyphenyl) ethanamide, also known as paracetamol) is a basic bioactive compound containing an *N*-acetylated aromatic amine with the acyl group bonded to the nitrogen atom (Fig. 1) [24].

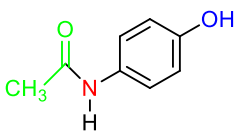


Fig. 1. The chemical structure of acetaminophen.

The benzene ring core of the aromatic amine is substituted by one –OH group. The hydroxyl group and the amide moiety's nitrogen atom (N) are bonded to the benzene nucleus in the para position [24]. The presence of these active groups makes the aromatic group very reactive during electrophilic aromatic substitution reactions. The acetaminophen molecule is highly conjugated because of the lone pair on the carbonyl oxygen, nitrogen, hydroxyl oxygen, and the aromatic pi cloud and p orbital on the carbonyl carbon. This reduces the basic value of nitrogen and oxygen atoms, making the hydroxyl group acid group via delocalization of the charge on the phenoxide ion [25]. The molecular formula of acetaminophen is $C_8H_9NO_2$, with a molecular mass of 151.18 g/mol [24].

Paracetamol synthesis involves converting phenol via electrophilic aromatic substitution to para-substituted nitrophenol in the presence of dilute sulphuric acid and sodium nitrate (Fig. 2). The nitro moiety of the nitrophenol is converted to an amine by direct hydrogenation or sodium borohydride reduction (Fig. 3). The *para*-aminophenol, therefore, reacts with acetic anhydride to form acetaminophen [26–28]. During this reaction, the acetic anhydride's carbonyl group (which is electrophilic) is attacked by the nucleophilic amine (Fig. 4). A new and easy method of acetaminophen synthesis involves a diazotization reaction. The reaction starts with a nitration reaction of acetanilide to form p-nitro acetanilide, followed by a reduction of the final product to produce p-amino acetanilide, creating a diazonium salt which then reacts with 10% of 2.5 M sodium hydroxide [29].

4. Possible effects and biochemical changes of acetaminophen after heating

Heat has a serious effect on the stability of acetaminophen. Under dry conditions, acetaminophen is very stable [30]. However, in moist conditions and at elevated temperatures, acetaminophen loses its analgesic/antipyretic properties and degrades rapidly into an organic compound known as *p*-aminophenol, which subsequently undergoes additional oxidative changes to other toxic intermediates [11,30]. Other intermediates of acetaminophen degradation include hydroquinone, *p*-nitrophenol, *N*-acetyl-benzoquinone imine, and 1, 4-benzoquinone [11,31]. These intermediates are highly toxic to the liver and the kidney and are challenging to degrade using conventional, expensive methods [11,31,32]. The degradation of acetaminophen in aqueous solutions is pH-dependent and follows first-order kinetics [30]. The mode of formation, toxicity, and structures of these intermediates are summarized in Table 1.

5. Proposed mechanism of the role of acetaminophen in meat tenderness

Along with appearance and juiciness, tenderness is among the essential qualities consumers look out for in meat products. This is because the satisfaction and taste perception are highly dependent on this factor, and it determines to a large extent if such products will enjoy continued patronage [40,41]. It is proposed that postmortem meat tenderness results from the fragmentation of muscle structural and associated proteins (e.g., myosin, actin, collagen, and elastin) via the activity of endogenous proteases and the continued degradation of cytoskeleton proteins and energy metabolism [42]. These proteins' degradation levels are associated directly or indirectly with the expression levels of various apoptotic molecules such as the calpains, caspases, and heat shock proteins [43]. Many techniques have been employed to enhance postmortem meat tenderization. They include aging tenderization and enzymatic techniques involving modifying endogenous protease systems and the addition of exogenous proteases to degrade muscle proteins responsible for meat toughness [44,45]. There are also chemical processing techniques involving the addition of salts, organic acids, and other chemical additives within required limits. Other techniques of tenderization include low-temperature long-time cooking, microwave heating, and high-pressure and ultrasonic processing [46].

Many food vendors have continued using acetaminophen for meat tenderization despite numerous warnings from health professionals about the health implications of this practice. Although no systematic research has elucidated the exact mechanisms by which acetaminophen contributes to postmortem meat tenderness, we propose that the mechanism could be similar to that of the postmortem aging tenderization effect. Postmortem aging significantly affects meat tenderness, flavor, and water-holding capacity. Aging tenderization involves several processes, including activating apoptosis (via activation of caspases), activating the calpain system, increasing reactive species generation and oxidative stress, increasing intracellular Ca^{2+} release, and reducing pH [46]. All aspects of apoptotic signaling in the cell are mediated directly or indirectly by the action of caspases. Procaspases are considered the best indicators of apoptosis in cells [43,47].

The primary step in converting muscle to meat is the induction of apoptosis mediated by activating different caspases, including caspase-3 and caspase-9 [46,47]. Apoptotic pathways trigger the activation of intracellular proteases and endonucleases, which are responsible for cell breakdown. It is reported that increased caspase-3 activity during apoptosis influences the calpain system by inhibiting the activity of the calpain inhibitor calpastatin during postmortem meat tenderization. Kato and his colleagues [48] showed that caspases promote calpain activity by suppressing the activity of its main inhibitor, calpastatin, in human Jurkat T cells during apoptosis. The same phenomenon was reported by Isabella Pörn-Ares et al. [49]. They reported that the 110–120 kDa calpastatin

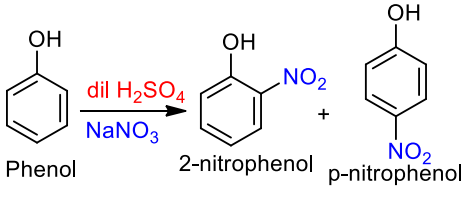


Fig. 2. Nitration of phenol.

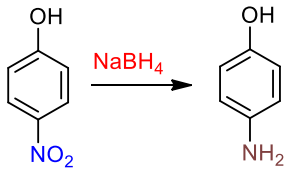


Fig. 3. Reduction of *p*-nitrophenol.

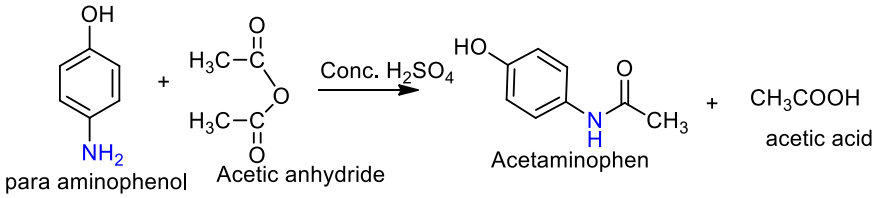
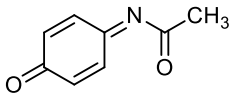
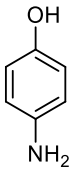
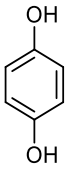
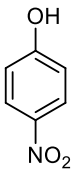


Fig. 4. Acylation of *para*-aminophenol.

Table 1
Examples and mechanism of toxicity of some degradation products of acetaminophen.

	Products of acetaminophen degradation	Mode of formation from acetaminophen	Mechanism of toxicity	Structure of the metabolite	References
1	*N*-Acetyl-*p*-benzoquinone imine	Oxidation	Produces free radicals in an organism which in turn leads to oxidative damage, induces apoptosis and necrosis in cells		[33–35]
2	*p*-aminophenol	Hydrolysis of acetaminophen	Causes nephrotoxicity and teratogenic toxicity. Can cause methemoglobinemia.		[36]
3	hydroquinone	Hydrolysis and oxidation	Toxicity involves the generation of reactive oxygen species (ROS)		[37]
4	*p*-nitrophenol	Hydrolysis of acetaminophen and oxidation of *p*-aminophenol	Carcinogenic and induces genotoxic effects on cells and cause respiratory complications		[38,39]

protein of Jurkat T-lymphocytes and U937 monocytic leukemia cells was cleaved to a 65–70 kDa form after the induction of apoptosis with san anti-CD95 monoclonal antibody, staurosporine or tumor necrosis factor (TNF) attributing this effect to the activity of caspase-3 [50].

The calpain system consists of endogenous proteases implicated for their role in the postmortem degradation of muscle protein and has been linked to meat tenderness. They are a large family of calcium-dependent cysteine proteases optimally active at neutral pH. The most studied isoforms of this enzyme system are the myofibril-bound μ-calpain, the cytosolic *m*-calpain requiring a higher Ca^{2+} concentration for its activity than the former, and calpastatin, which acts to inhibit the activities of the calpains [42,51]. Calpains promote meat tenderness by degrading (by protease hydrolysis) essential proteins in myofibrils (e.g., nebulin, titin, troponin-T, and desmin) responsible for meat toughness, causing myofibril fragmentation and meat tenderness [46]. On the other hand, calpastatin inhibits calpain catalytic activity by preventing its membrane binding capacity and the activation of protease hydrolysis [52]. The postmortem meat tenderness rate depends on the expression levels of calpain/calpastatin in the meat. Calpastatin content of muscle

decreases gradually after slaughter, and its rate of degradation or inactivation is related to the expressive proteolysis in muscle. Increased calpain/calpastatin ratio will increase protease hydrolysis, muscle tenderness, and vice-versa [52].

Metabolism of acetaminophen is associated with generating toxic metabolites with high oxidant capacities, which overwhelm cellular antioxidant systems, resulting in significant oxidative stress conditions [53,49]. Increased oxidative stress promotes the initiation of apoptotic signaling by increasing factors such as cytochrome *c* displacement and the caspase cascade. Several studies have reported apoptosis activation as one of the mechanisms of acetaminophen toxicity. In two different studies, Kon and colleagues reported that incubation of rat hepatocytes with a high dose of acetaminophen resulted in caspase activation and apoptosis [54,55]. In other studies, acetaminophen overdose caused significant reductions in procaspases −3, −8, and −9 indicating the activation of the related caspases [45,56]. Kučera et al. [57] also reported that acetaminophen overdose increased caspase-3 activity in rat hepatocytes. Therefore, it is logical to speculate on the possible mechanism of acetaminophen-mediated tenderization in meat by directly activating the apoptotic signaling cascade and indirectly influencing meat's calpain/calpastatin activities.

6. Biotransformation of acetaminophen residues and metabolites from consumption of APAP-tenderized meat in humans

Acetaminophen is a common drug for analgesic and antipyretic activities without toxicity under prescribed conditions. However, due to APAP misuse, abuse, and overdose, several forms of toxicity affecting the hepatic and nephron systems have been reported due to APAP metabolites or bio-transformed products [58]. Although there has not been any study that has experimentally investigated the events of biotransformation of APAP residues and metabolites consumed from tenderized meat, we present this section as a perspective from countless evidence from animal studies, and food ingredients and other common drug interactions with APAP, possibly consumed alongside with the tenderized meat.

6.1. Biotransformation and mechanism of toxicity of acetaminophen (APAP)

When APAP is taken within the therapeutic dose and safe range – below 4 g/day for adults and 40–75 mg/kg/day for children, it performs its normal analgesic and antipyretic functions either majorly via the eicosanoid pathway (inhibitory action on prostaglandins synthesis), or through other minor pathways (endocannabinoid, serotonergic, and nitric oxide) as described by recent studies [25,59]. On completion of the analgesic activities, the body gets rid of the drug via the detoxification and metabolic activities of the liver and its enzymes [60]. Although APAP could be administered intravenously, it has been reported to have high bioavailability (88%), reaching its peak blood plasma concentration around 90 min after oral intake. Studies have shown its half-life in the blood plasma to be between 1.5 and 2.5 h before transportation to the liver for complete detoxification [58].

In the liver, the APAP, through glucuronide and sulfate conjugation, are bio-transformed into their inactive APAP-glucuronide and APAP-sulfate conjugates and transported to the kidney through the blood for excretion as urine [61]. Experiments of urine analysis in individuals administered with less than 4 g per day of APAP showed about 52–57% of APAP-glucuronide metabolite, 30–44% APAP sulfates, and less than 5% unconjugated [58]. Other studies have reported that some of the unconjugated fractions of APAP (5–10%) in the liver are oxidized to an active and toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI) [53]. However, at a normal therapeutic dose of APAP, the NAPQI and other toxic metabolites are overcomed by the antioxidant activities of glutathione (GSH), which bind to the metabolites, inactive them, and foster that excretion through the urine as cysteine and mercapturic acid conjugates [60].

When APAP intake is over the supra-therapeutic dose, the sulfation pathway gets saturated, followed by the glucuronidation pathway, causing an elevated amount of unconjugated APAP in the plasma and the urine. Consequently, increased oxidation products and toxic metabolites from the unconjugated APAP overwhelm the GSH antioxidant system's capacity, resulting in liver damage, renal failure, and even death [49]. NAPQI, one of the toxic oxidative metabolites, has been reported to target mitochondrial protein and ion channels, resulting in energy depletion, ion imbalance, and cellular death [62,63]. Studies have shown that administering *N*-acetylcysteine (NAC) within 8–10 h of APAP ingestion rescues hepatotoxicity to only 5% [64,65]. A study on the chronic exposure of APAP to *Daphnia magna* reported an upregulation of the detoxification gene within 24–48 h. In contrast, prolonged exposure resulted in the downregulation of detoxification genes CYP360A8 and CYP314 and the physiological and reproductive parameters in *D. magna* [66]. Hence, acute APAP toxicity can be tackled, whereas worrisome challenges and destruction of hepatic cells can result from prolonged or chronic exposure.

In detail, the glucuronidation reaction is usually mediated by the UDP-glucuronosyl transferases (UGT), Sulfation by cytosolic sulfotransferases (SULT), and oxidation to NADQI by Cytochrome P450 enzymes [61]. Moreover, these different enzymes are controlled by several polymorphic genes that express different isoforms based on APAP concentration. For instance, human hepatocytes have been reported to express UGT1A1, UGT1A6, UGT1A9, and UGT2B15 (different isoforms of UGT) at different concentrations of APAP [67]. While UGT1A6 is predominant at a low concentration of APA, UGT1A1 and UGT1A9 are predominant mostly at high and toxic doses [68]. Similarly, CYP2E1, CYP1A2, and CYP2A6 are the different cytochrome P450 isoforms implicated in oxidizing APAP to NAPQI at toxic do [69]. In contrast, CYP3A4 was controversially agreed from different in vitro and in vivo experiments to be involved in low-dose APAP bioactivation [58]. Moreover, organs such as kidneys having a reduced Cytochrome P450 activity, prostaglandin H_2 synthases (PTGS) have been implicated in the oxidation of unconjugated APAP to NAPQI and NAPSQI (*N*-acetyl-*p*-benzosemiquinone imine). Conversely, Isoforms activities of SULT vary from fetal to adult. While SULT1A1 and SULT1A3/4 are enzymes for Sulfation in adult humans, SULT1E1 and SULT2A1 are predominant in fetal microsomal and hepatic tissues [63]. Hence, a lower saturation point of APAP concentration for the fetal isoforms of the SULT enzymes exists compared to the adult variants.

At a normal dosage of APAP, the minimal NAPQI (<5%) generated due to the activities of CYP450 enzymes are mopped up either by the spontaneous conjugation to GSH or catalyzed by Glutathione-*S*-transferases (GSTs) enzymes [62]. In the spontaneous

non-enzymatic reactions, 3-(Glutathione-*S*-yl)-acetaminophen (APAP-GSH) conjugate, free APAP, and oxidized glutathione disulfide (GSSG) is the end product. In contrast, the enzymatic conjugations yield only APAP-GSH and free APAP [70]. Similar to other microsomal and hepatic enzymes, different isoforms for GST correlate with either a reduced APAP dosage or an increased toxic dose [71]. In addition to the major pathway of metabolism of acetaminophen, there exist other minor pathways such as the deacetylation pathway - catalyzed by *N*-deacetylase to generate *p*-aminophenol of APAP [72], and thiomethyl shunt pathway – catalyzed by thiomethyltransferase to yield APAP-thiomethylconjugate, which have an extended half-life in the plasma [73,74]. Several studies have implicated *p*-aminophenol in cases of nephrotoxicity, especially in rodents. Moreover, other studies have discovered the conjugation of *p*-aminophenol to arachidonic acid yielding *N*-arachidonoylphenolamine (AM404) in the brain. The conjugation reaction is catalyzed by the Fatty Acid Amide Hydrolase (FAAH) enzyme, and the AM404 product has been reported to possess a great affinity for the TRPV1 receptor of the brain and spinal cord, mediating pro-inflammatory and painful stimuli [61,75]. Therefore, it is evidence that APAP concentration affects the expression of different microsomal/hepatic enzymes, resulting in strains and damage to the liver cells.

In conclusion, the regulatory pathway and mechanism involved in APAP-induced toxicity have not been completely elucidated. New findings have implicated some long-chain ncRNA such as HNF1α-AS1 and HNF4α-AS1 to play regulatory roles in controlling activities of CYP450 systems and as well as other detoxification enzymes [76]. Despite the complexity of pathways, proteins, and genes involved, the majority of studies both on in vitro cell lines, animal models, and human subjects still point towards the detrimental impacts of APAP on liver and kidney tissues, to a lesser extent, reproductive general physiological signaling.

6.2. Acetaminophen interactions with tenderized meat components and possible co-consumed foods or drinks – suggestive mechanism of enhanced toxicity

Acetaminophen (APAP) has gained a secondary function as a meat tenderizing agent for many food vendors in several developing

Table 2
Interaction with food substance possibly consumed with APAP-tenderized meat.

Meat components, other Food ingredients, drinks and drugs	Effects on APAP Toxicity	Genes and proteins implicated	Dosage/treatments	References
Alcohol (Beer, Spirit, Red wine and others) and APAP-tenderized meat	- Hepatotoxicity even at therapeutic doses - NAPQI accumulation - Alcohol and APAP competition for liver detoxifying enzymes - Acute interstitial nephritis - mortality	↓GSH ↑ CYP2E1 ↑CYP3A	≥4.0 g APAP/day in human	[79,80, 83–86]
Fasting (Food deprivation) before consumption of APAP-tenderized meat	- hepatocellular necrosis - increase in NAPQI	↑ *CYP2E1* ± *Ugt1a6* ± *Sult1a1* ± *Gstm1*	800 mg APAP/kg of rat a) 16 h of fasting b) 30% ad libitum food restrictions.	[81,82,84]
Grapefruit juice and consumption of APAP-tenderized meat	- increase the bioavailability of APAP - inhibits p-gp - Increased in Serum APAP - the decreased half-life of APAP in serum	↓CYP3A4 ↓p-gp	10–100 mg/kg of APAP orally fed to BALB/c mice	[87]
Ginger spices (*Zingiber officinale*) in APAP-tenderized meat	- Increase in liver marker enzymes - hypoalbuminemia - hyperglobulinemia - decrease in GSH and antioxidant enzymes	↓GST ↓ GR ↓GPX ↑AST, LDH, ALP and GGT	1 g of APAP/kg body weight of rat for 21 days 1% w/w ginger in diet	[88]
Free cholesterol (obesity, fat diet)	- increase APAP induced hepatotoxicity via the TLR9/inflammasome pathway - accumulation of free cholesterol in Liver sinusoidal endothelial cells (LSECs) - disrupt Rab7 membrane trafficking recycling mechanism - Enhance TLR9 signal transduction - Cholesterol impairs membrane transport of TLR9 protein; hence elevation of cleaved TLR9 protein	↓active Rab7 protein ↑cleaved TLR9 protein	500 mg APAP/kg body weight intraperitoneally administered to mice after starvation for 15 h.	[89]
Vitamin C (fruits and fruit juices) and APAP-tenderize meat	- Vit C (Ascorbic acid) compete for available sulfate in the body - Inhibit sulfate conjugation of APAP - Increase APAP biological half-life from 2.3 ± 0.2 to 3.1 ± 0.5 h	–	Oral administration of 3 g ascorbic acid and 1 g of APAP after 1.5 h	[90]

↑ - increase or upregulation; ↓ - decrease or downregulation; ± - no significant change in effect: Ugt1a6 - UDP-glucuronosyltransferase 1A6; Sult1a1 - sulfotransferase 1A1; Gstm1 - glutathione *S*-transferase M1; GR - glutathione reductase, GPx - glutathione peroxidase, and GST - glutathione-*S*-transferase; GGT - Gamma-glutamyl Transferase.

countries [11]. However, the practice continued due to the paucity of research findings, publications, and awareness campaigns on the detrimental effects of APAP when consumed alongside tenderized meat. This section presents several possibilities and routes of toxicities of APAP in tenderized meat on humans.

Generally, many vendors that adopt APAP for tenderizing meat do not quantify the amount used per time. However, adult humans can only accommodate a limited amount (less than 4 g) of APAP in their body system per day [77]. Hence, individuals who consume this meat are unaware of the quantity of APAP residues ingested into their bodies and possibly be exposed to a chronic level of APAP, depending on the amount and frequency of consumption of such meat tenderized with APAP. Therefore, it is not out of place to state that APAP-tenderized meat is a potent risk factor for hepatic and nephro-toxicities and several physiological and metabolic distortions [78].

Although APAP has been reported to be very stable even up to 140–160 °C, depending on the cooking system which is used - such as pressurized steaming or roasting after a brief tenderization, the APAP in the meat sample could be degraded and oxidized, yielding several metabolites such as *p*-nitrophenol, hydroquinone, *p*-aminophenol and *N*-Acetyl-*p*-benzoquinone imine [30]. These degraded products pose another toxicity level and risk to human health, as described in Table 1.

A more complex route of toxicity could emerge from interactions with APAP residues and its metabolites with the component of meats, cooking ingredients, and spices or drinks consumed alongside. Summarized in Table 2 are studies of the possible mechanism of interaction of different substances such as alcohol, grapefruit, ascorbic acid, and spices like ginger possibly consumed with APAP-tenderized meat. Several studies have reported that alcohol intake with APAP or APAP intake by chronic alcoholics could result in severe acute hepatic toxicity even at therapeutic doses [79]. Generally, alcohol competes with APAP for liver detoxifying and anti-oxidant enzymes such as GSH. The co-consumption of alcohol and APAP from tenderized meat can lead to the upregulation of some cytochrome P450 genes, such as CYP2and CYP3A, which are known to foster liver damage [80]. Similarly, consumption of APAP-tenderized meat after fasting conditions could result in similar toxicity due to the activities of ketone bodies [81]. It was reported that rats administered with APAP after a 16 h fast, as well as those deprived of about 30% of their normal ad libitum feed, led to an upregulation of the *cyp2e1 gene, although other genes like Ugt1a6, Sult1a1,* and *Gstm1* were not affected [82].

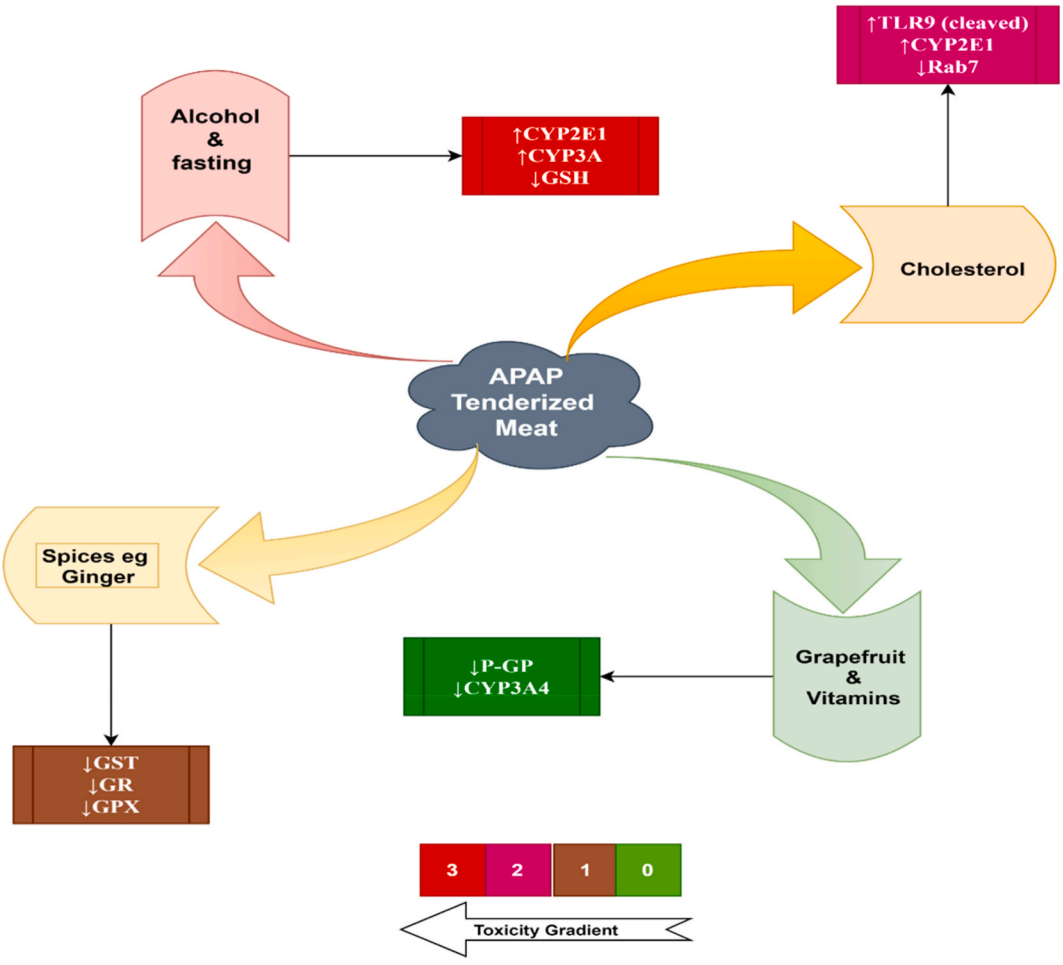


Fig. 5. APAP-tenderized meat interaction with food components and associated toxicity.

Spices used for cooking meat, such as Ginger (*Zingiber officinale),* have been reported in the past to heighten the toxic consequence of APAP. A study by Lebda et al. [91] reported a drastic downregulation of GST, GR, and GPX while upregulation of liver marker enzymes such as AST, LDH, ALP, and GGT in rats fed with 1% w/w of ginger as well as 1 g of APAP for 21 days. On the contrary, grapefruit juice has been reported to counter the toxic consequences of APAP and could be adopted as a home remedy for acute APAP toxicities. In BALB/c mice, grapefruit juice improved the bioavailability of APAP by inhibiting the gastrointestinal *p*-glycoprotein, hence shortening the half-life of the APAP in the animal. Furthermore, CYP3A4, a cytochrome P450 enzyme, was significantly downregulated than normal control [87]. Similarly, several classes of water and fat-soluble vitamin have been reported to possess ameliorative effects on APAP-induced toxicity [92,91]. However, other different studies on ascorbic acid showed contrasting results [93,90].

High fat and cholesterol levels have been reported to increase APAP-induced hepatotoxicity via the TLR9/inflammasome pathway [89]. Accumulation of free cholesterol in liver sinusoidal endothelial cells (LSECs) disrupts the Rab7 membrane trafficking recycling mechanism, enhancing TLR9 signal transduction. Cholesterol impairs membrane transport of TLR9 protein, hence elevation of cleaved TLR9 protein, which consequence of inducing the hepatotoxic cascade of APAP [89].

Although there are no specific studies on toxicities emerging from APAP-tenderized meat, it is vivid that the nature of interactions of food components and APAP is complex, and there are possibilities of enhanced toxicities, as shown in Fig. 5. We, therefore, recommend more studies to understand the safety or toxic profile of adopting APAP in tenderized meat.

7. Strategies for mitigating the abuse of acetaminophen by food vendors

The use of acetaminophen for tenderizing meat for food can be referred to as an abusive drug repurposing. Although the high dosage allowance (<4 g/day) in an adult human, its unscrupulous use in food processing possibly fosters consumption of more than the required dosage, hence drug abuse [94]. Conc concerted efforts are needed to mitigate APAP abuse in meat tenderizing. Presented in this section are suggestions to end the menace possibly.

7.1. A formal ban on the use of APAP for meat tenderizing

There is a need for governments of nations and institutions to place a formal ban on APAP for tenderizing meat. More so, setting up enforcement and monitoring agencies to foster adherence to the laws by food vendors is a step in the right direction. Some other toxicants of foods, such as calcium carbide for fruit-ripening and some azo-dyes in food products, have been successfully banned in many developed and developing countries [95]. Adopting strategies that ensured the successful ban of other well-known toxicants could yield similar results in enforcing the ban on the abusive use of APAP by food vendors.

7.2. Education and awareness campaign

Most food vendors use APAP to tenderize meat because they are cheap, readily available, and cost-effective. However, many of these vendors are unaware of the negative implication of APAP from tenderizing meat samples on human health. Therefore, creating awareness through campaigns on social media, television programs, radios, and even newspapers could drastically reduce the practice. Studies have shown that poor education and awareness contribute tremendously to the heightened use of many toxicants in food processing [96]. Hence, educating food vendors and the general populace of a nation would create a more enlightened society that deceases from such ill-practice of adopting APAP for meat tenderizing.

7.3. Promotion of the use of natural tenderizers

Promoting studies on natural and healthy products as an alternative to acetaminophen can also be helpful. Studies have shown that papain from papaya extract, bromelain from pineapple, curcumin from turmeric, and many plant products have interesting meat tenderizing abilities [97–99]. These natural products are non-toxic and least affect the sensory properties of meat when compared to APAP. Therefore, if a better and more promising alternative is brought to many foods vendors' awareness, the menace of adopting APAP for meat tenderizing would drastically be reduced.

7.4. Developing an easy and customer-friendly detection method of APAP in meat

Several analytical technologies have been developed to detect APAP in other drugs, human serum, and urine samples. Some of these technologies use electrometric, potentiometric, or voltammetry principles to detect paracetamol [100,101]. Moreover, recent studies have reported other sensing technologies, such as piezoelectric and ratio-metric sensing, with tremendous success in detecting paracetamol [102]. Despite the success of these technologies, none have been adopted for detecting APAP in meat samples. Moreover, the complexities of their protocol make these technologies not feasible for a quick check of meat bought by customers from food vendors. Therefore, there is a need to develop an easy detection approach for APAP in tenderizer meat. For instance, the development of detection strips and the adoption of AI techneorology to differentiate between sensory qualities of APAP-tenderized meat and other means of meat tenderizing can be a step in the right direction [103,104].

8. Conclusion

Meat remains a major source of proteins, minerals, fats, vitamins and so many other nutritional needs of man. The continuous quest for meat will continuously increase upwards so as to serve the overwhelming global population growth. The tenderness and the nutritional values in meat is the hallmark of consumers' acceptability. However, many food vendors have thrown caution to air and resort to using acetaminophen in meat tenderizations without regards to the health and hazardous implications to consumers. Special attention should be paid to this growing trend so as to savage the wholesomeness of meat and likewise save the lives of uninformed consumers.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data included in article/supplementary material/referenced in article.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviation

APAP	Acetaminophen or Paracetamol
COX	Cyclooxygenase
PGH_2	Prostaglandin H_2
HETEs	hydroxyeicosatetraenoic acids
5-HT	5-hydroxytryptamine
TRPV1	transient receptor potential vanilloid 1
CB1	cannabinoid 1
THC	tetrahydrocannabinol
NAPQI	*N*-acetyl-*p*-benzoquinone imine
GSH	Glutathione
NAC	*N*-acetylcysteine
SULT	cytosolic sulfotransferases
UGT	UDP-glucuronosyl transferases
CYP	Cytochrome P450
AM404	*N*-arachidonoylphenolamine
FAAH	Fatty Acid Amide Hydrolase
THC	Tetrahydrocannabinol

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