

Antiplatelet and Antioxidant Activities of Tomato

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Abstract Tomato, botanically known as *Lycopersicon esculentum*, is a food crop used throughout world in different cultures. Traditionally, various cardiovascular and inflammatory ailments are cured by fruit of this plant. But this has been done without any knowledge about its exact mechanism in these diseases, especially in thrombotic conditions. This study has been designed to investigate the potential mechanisms used by *Lycopersicon esculentum* fruit to provide relief in these diseases. A crude fraction of *Lycopersicon esculentum* fruits was prepared and then separated into n-hexane, chloroform and aqueous fractions. These fractions were screened for the presence of activities against arachidonic acid (AA) metabolism and agonist-induced human platelet aggregation. These fractions were also investigated for their potential to enhance the activities of antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx). Platelet aggregation was monitored using turbidometric principle, while AA metabolism was studied using radiolabelled AA. Antioxidant enzymes were measured by commercial kits using spectrophotometer. The aqueous fraction of *Lycopersicon esculentum* was mostly active against cyclooxygenase pathway of AA metabolism while chloroform was the only fraction possessing significant activity against lipoxygenase pathway. Aqueous and n-hexane fraction seem to have concentrated compounds responsible for elevating SOD activity while n-hexane was the most potent against PAF and the only fraction exhibiting potent activity against collagen-induced platelet aggregation. Compounds responsible for elevating GPx activity seems to be distributed throughout various fractions of tomato. The results demonstrate that anti-inflammatory and cardiovascular effects of *Lycopersicon esculentum* are mediated through multiple pathways. The compounds responsible for these pharmacological actions were however, distributed throughout various fractions of *Lycopersicon esculentum*.

Keywords: *Lycopersicon esculentum*, tomato, cyclooxygenase, lipoxygenase, superoxide dismutase, glutathione peroxidase, platelet aggregation

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1. Introduction

Tomato (*Lycopersicon esculentum*) is an important food plant which, besides having one of the highest consumption rates in the world, has significant medicinal value owing to the presence of multiple bioactive compounds [1]. Important phytochemical constituents of *Lycopersicon esculentum* include flavonoids, beta-carotene, phenols, and lycopene [2]. Many of the medicinal actions of *Lycopersicon esculentum* are explained on the basis of lycopene [3,4]. Many nutrients such as vitamin C, potassium and polyphenols are also found in *Lycopersicon esculentum* in appreciable concentration. Additionally, *Lycopersicon esculentum* contains significant quantities of gamma amino butyric acid [5,6].

Among the many medicinal uses of *Lycopersicon esculentum* practiced by the traditional healers in India include its emollient and carminative actions, as well as intestinal antiseptic functions. *Lycopersicon esculentum* is also traditionally used in ulcerative stomatitis, dermatopathy, asthma, neuropathy and general debility [7]. Anti-nociceptive and anti-inflammatory activities of *Lycopersicon esculentum* are also reported [8]. Various polarity based extracts of *Lycopersicon esculentum* obtained at low temperature show cytotoxic and antioxidant activities [9]. *Lycopersicon esculentum* products prevent lipid peroxidation, and this effect was observed along with a reduction in prostaglandin F_{2α} [10]. The methanolic extract of the *Lycopersicon esculentum* leaves showed more potent anthelmintic effect than the standard albendazole [11]. The risk of chronic diseases including cancer and cardiovascular disease is reduced by the use of

Lycopersicon esculentum and its related food products [12,13]. Antibacterial activity of *Lycopersicon esculentum* pulp oil is reported against gram positive and gram negative organisms as well as against fungi and this effect was associated with the presence of a complex of organic acids [14].

The most important constituent of *Lycopersicon esculentum* and its related products-lycopene is also among the most potent antioxidants [15]. In patients with prostate cancer, the use of *Lycopersicon esculentum* or lycopene was associated with lower serum prostate-specific antigen concentrations, increased apoptosis and reduced DNA damage. Overall it resulted in fewer tumors compared to the controls [3,16,17,18]. Antioxidant, antimicrobial and anti-inflammatory, anticonvulsant, anticancer, antifungal and antiviral activities of flavonoids from *Lycopersicon esculentum* are also reported [19-23].

The fruit of *Lycopersicon esculentum* is consumed in various heart and inflammatory conditions for providing relief but the underlying mechanism of its therapeutic action remain unknown [7]. A number of medicinal plants employed traditionally in inflammatory and cardiovascular ailments have been reported to possess activities against arachidonic acid (AA) metabolism and agonist-induced human platelet aggregation [24,25]. Therefore, in the present investigation, we screened various fraction obtained from the fruit of *Lycopersicon esculentum* against agonist-induced human platelet aggregation and AA metabolism mediated by cyclooxygenase (COX) and lipoxygenase (LOX). Furthermore, these fractions were also investigated for their effects on activities of antioxidant enzymes-superoxide dismutase (SOD) and glutathione peroxidase (GPx). To our knowledge, these activities have not been reported for the fruit of *Lycopersicon esculentum*.

2. Materials and Methods

2.1. Chemicals

Most of the chemicals used in this investigation were purchase from Sigma-Aldrich, USA, while ¹⁴C arachidonic acid was purchased from Amersham Biosciences, sodium phosphate-mono and dibasic from Merck, and acetic acid and citric acid from BDH. All the chemicals used in the investigation were of analytical grade.

2.2. Extraction of Plant Material

Lycopersicon esculentum fruit (5kg) was purchased from the market and authenticated by a botanist at department of plant sciences, Kohat University of Science & Technology, Kohat, Pakistan. A specimen of the fruit was kept in the herbarium of department of pharmacy of the same university. *Lycopersicon esculentum* fruit was dried in the shade to prevent possible denaturation of heat sensitive phytochemicals. Dried *Lycopersicon esculentum* fruit was crushed to powder and about 1400 g of powder so obtained, was subsequently immersed in aqueous methanol. This mixture containing the powdered *Lycopersicon esculentum* fruit in 5 liters of aqueous methanol was left

for 24 hours at a temperature of 4°C [26]. The next day, mixture was first filtered and then put in a rotary evaporator to remove the aqueous methanol. The resulting crude extract of *Lycopersicon esculentum* fruit had a dark brown color.

2.3. Fractionation of the Crude Extract

Crude extract was further divided into three different polarity based fractions. In brief, separating funnels were used to make these polarity based fraction. Crude extract (450 grams approx.) was dissolved in 500 ml of water and shaken vigorously. The mixture was placed in a separating funnel and 500 ml of n-hexane was also added to it. After strong shaking the mixture was left for about half an hour at room temperature to allow two layers separate. The upper n-hexane fraction was acquired and another 500 ml of n-hexane solvent added to the remaining mixture. This fractionation process was repeated thrice for n-hexane fraction and then for chloroform fraction. After the fractionation process for chloroform was completed, the remaining mixture was termed as aqueous fraction. All three fractions-aqueous, chloroform and n-hexane were dried in rotary evaporator to get concentrated fractions.

2.4. Antiplatelet Activity

2.4.1. Arachidonic Acid Metabolism by Human Platelets

The effect of *Lycopersicon esculentum* and its various fractions on the formation or inhibition of AA metabolites was measured as previously described [27]. Plasma in the concentrated form was obtained from the clinical laboratories of the Aga Khan University Hospital, Karachi which was then processed before starting any experimentation. This processing included centrifugation of the plasma at 1200 g for 20 minutes to further concentrate the plasma and to obtain a fraction known as platelet rich plasma (PRP). Phosphate buffer was used twice to wash the PRP and then was resuspended in the same buffer but this time EDTA was not added to the buffer.

This suspension of PRP was homogenized with a polytron homogenizer at 4 °C for 15 seconds. After that, the homogenate was again subjected to centrifugation at 1200g for 20 minutes. After centrifugation, the supernatant was obtained and 300 µl of it was incubated with the various fractions of *Lycopersicon esculentum* and 10 µg unlabelled AA and 0.1 µCi [1-¹⁴C]AA to start the metabolism, which continued for 15 minutes at 37°C. This chemical reaction of AA metabolism was stopped by the addition of citric acid and ethyle acetate. Under standard recommended conditions, the organic layer was obtained and the dried. The residues were dissolved in appropriate solvents and resolved using thin layer chromatography (TLC) technique. The standards for all metabolites were plotted separately. The TLC plates were developed using appropriate development systems for various metabolites. The radioactive zones were located on TLCs and quantitation was done with a Berthold TLC linear analyzer and chromatography data system.

2.4.2. Preparation of Platelets

Platelets for aggregation studies were prepared by obtaining blood from healthy human volunteers who have not used any medication in the last 2 weeks. The blood obtained from these volunteers was mixed with 3.8% sodium citrate in a ratio of 1 to 9 and then mixed slowly. This mixture was concentrated by using centrifugation at 260g for 15 minutes. The supernatant was separated and known as platelet rich plasma (PRP). The remaining mixture was centrifuged at higher speed of 1200g for 10 minutes and again supernatant was collected which was known as platelet poor plasma (PPP). Phase contrast microscopy was used to count the number of platelets in PRP, and was between 2.5 and $3.0 \times 10^8 \text{ ml}^{-1}$ of plasma [28], platelet aggregation studies were carried out at 37°C while platelets were centrifuged at 20°C.

2.4.3. Measurement of Platelets Aggregation

After preparing platelets, aggregation studies were carried out using 450 μl of PRP [29]. By adding platelet agonist and test sample, the final volume of the assay was made upto 500 μl . Platelets were aggregated using four separate inducing agents namely; PAF (0.8 μM), AA (1.7 mM), ADP (2.2 μM), and collagen. A test fraction was first added to PRP at least 2 minutes before the addition of a platelet aggregating agent. Platelet aggregation or lack of it was monitored for 5 minutes and was measured by a change produced by the transmission of light as a function of time [30]. After measuring platelet aggregation induced by 4 different agonists, dose response curves were constructed and IC_{50} values were calculated for all test fractions against each platelet agonist.

2.5. Antioxidant Activity

2.5.1. Glutathione Peroxidase Activity Determination

The activity of GPx was measured using special kits and as per manufacturer's instructions. Briefly, as described previously [31], the antioxidant assay starts with adding the test fraction of *Lycopersicon esculentum* in a solution containing the substrate- t-Butyl-hydroperoxide, nicotinamide adenine dinucleotide phosphate (NADPH) and glutathione. Bringing together reduced forms of NADPH and glutathione form the basis of this reaction. Reducing the substrate begins after initiating the reaction and was detected by observing a change in absorbance measured at 340 nm. The activity of GPx was finally measured using glutathione as co-substrate.

2.5.2. Superoxide Dismutase Activity Determination

The activity of SOD was measured using special kits and as per manufacturer's instructions. Briefly, as described previously [32], the antioxidant assay starts with adding the test fraction of *Lycopersicon esculentum* in a solution containing the substrate. A formazane dye is produced from the substrate 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride (INT). Xanthine and xanthine oxidase produce superoxide radicals. The

degree of inhibition of this reaction by test fractions determines the extent of SOD activity of that fraction. This is measured by detecting a change in the absorbance in the solution at 505nm.

2.6. Statistical Analysis

Student's t-test was used as a statistical tool to compare the means of different groups and the difference was considered statistically significant when $P < 0.05$.

3. Results

Crude extract displayed partial inhibition of platelet aggregation induced by PAF but showed more potent inhibition against AA (IC_{50} of $87 \pm 9 \mu\text{g}$ and $15 \pm 4 \mu\text{g}$ respectively) while no significant inhibition was observed against collagen and ADP up to a dose of 1mg. Just like crude extract, aqueous fraction showed partial inhibition of platelet aggregation induced by PAF but showed more potent inhibition against AA (IC_{50} of $74 \pm 9 \mu\text{g}$ and $12 \pm 4 \mu\text{g}$ respectively) while no significant inhibition was observed against collagen and ADP up to a dose of 1mg. Chloroform fraction, up to a dose of 1mg showed no significant inhibition of platelet aggregation induced by any of the four platelet agonists used in this study. The n-hexane fraction showed potent inhibition of platelet aggregation induced by PAF as well as by collagen (IC_{50} of $26 \pm 4 \mu\text{g}$ and $18 \pm 4 \mu\text{g}$ respectively) while no significant inhibition was observed against AA and ADP up to a dose of 1mg (Figure 1).

No significant activity was observed against LOX mediated AA metabolism up to a dose of 1 mg, however, formation of TXB_2 through COX was potently blocked (IC_{50} of $19 \pm 5 \mu\text{g}$). There was partial inhibition in the production of TXB_2 through COX (IC_{50} of $120 \pm 14 \mu\text{g}$), while significant blocking of LOX-mediated pathway of AA metabolism was observed as indicated by the inhibition of 12 HETE (IC_{50} of $28 \pm 5 \mu\text{g}$) (Figure 2).

Formation of TXB_2 through COX was potently blocked (IC_{50} of $18 \pm 4 \mu\text{g}$), whereas no appreciable effect was seen on 12 HETE up to a dose of 1 mg. Significant elevation of GPx activity was observed with crude extract (IC_{50} of $29 \pm 6 \mu\text{g}$) but no significant elevation of SOD could be detected up to a dose of 1mg. The positive control used for SOD and GPx activities was vitamin C and a $10 \mu\text{g}$ dose enhanced their activities to 217 ± 21 and 8664 ± 652 respectively. The activities of both GPx and SOD were significantly elevated by aqueous fraction of *Lycopersicon esculentum* (IC_{50} of $23 \pm 6 \mu\text{g}$ and $21 \pm 4 \mu\text{g}$ respectively). Just like crude extract, significant elevation of GPx activity was observed with chloroform fraction (IC_{50} of $32 \pm 7 \mu\text{g}$) but no significant elevation of SOD could be detected up to a dose of 1mg. No significant activity was observed against any of the metabolites of AA up to a dose of 1 mg. Just like the aqueous fraction, the activities of both GPx and SOD were significantly elevated by n-hexane fraction (IC_{50} of $18 \pm 46 \mu\text{g}$ and $36 \pm 5 \mu\text{g}$ respectively) (Table 1 & Table 2).

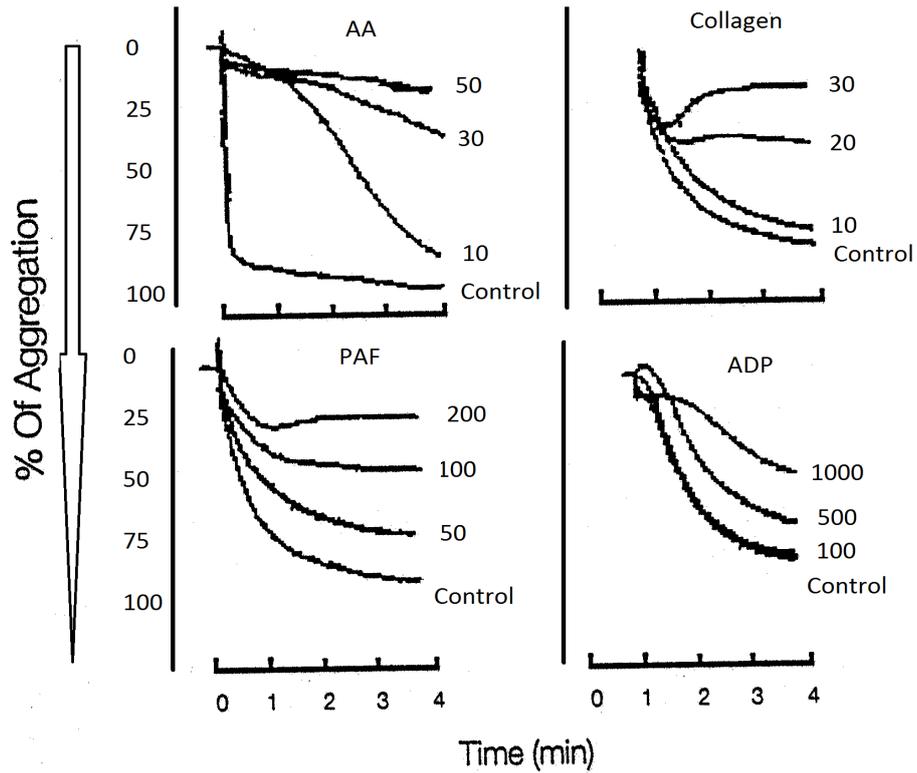


Figure 1. Representative scans of the effect of crude extract of *Lycopodium esculentum* and its fractions on platelet aggregation induced by various agonists, i.e. crude on AA, aqueous on PAF, chloroform on ADP and n-hexane on collagen

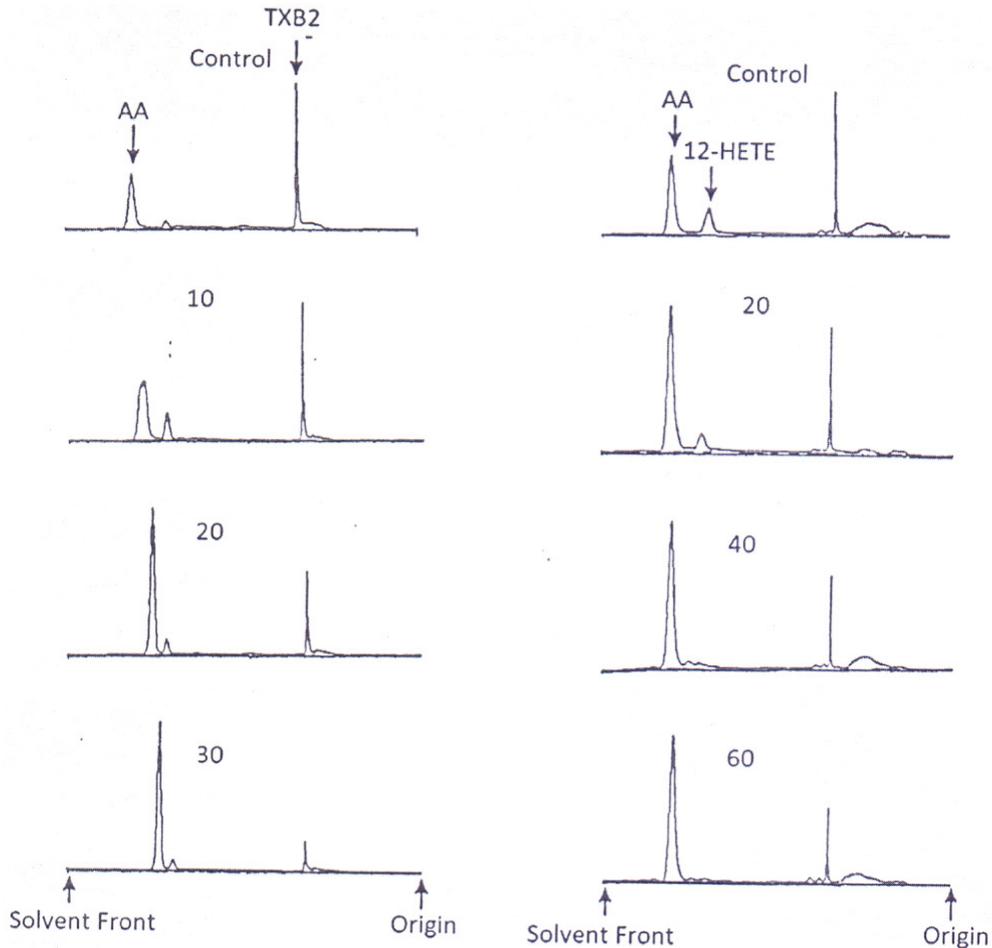


Figure 2. A representative scans of the effect of various fractions of *Lycopodium esculentum* on the formation of AA metabolites TXB2 (aqueous) and 12-HETE (Chloroform)

Table 1. IC50 (mean (SD)) of the crude extract of *Lycopersicon esculentum* and its fractions against various platelet agonists, AA metabolites and for antioxidant enzymes

S.No	Assay	Crude (μg)	Aqueous (μg)	Chloroform (μg)	n-Hexane (μg)
1	AA	15 (4)	12 (4)	1 mg	1mg
2	PAF	87(9)	74 (9)	1 mg	26 (4)
3	ADP	1 mg	1 mg	1mg	1 mg
4	Collagen	1 mg	1 mg	1mg	18 (4)
5	12-HETE	1mg	1mg	28 (5)	1mg
6	TXB ₂	18 (4)	19 (5)	120 (14)	1mg
7	SOD	1mg	21 (4)	1 mg	36 (5)
8	GPx	29 (6)	23 (6)	32 (7)	18 (4)

Table 2. The effects of the crude extract of *Lycopersicon esculentum* and its fractions on the activities of SOD and GPx. n = 6, *P <0.05 compared to saline

Extract/Fraction	Dose (μg)	SOD activity	Dose (μg)	GPx activity
Saline	10 μl	170 \pm 8	10 μl	5918 \pm 561
Crude	100	175 \pm 20	10	6103 \pm 615
	500	178 \pm 22	50	7336 \pm 535*
	1000	180 \pm 21	100	7919 \pm 758*
	10	182 \pm 19	10	6147 \pm 591
Aqueous	50	199 \pm 22*	50	7447 \pm 669*
	100	208 \pm 23*	100	7811 \pm 673*
	100	173 \pm 19	10	6201 \pm 652
Chloroform	500	175 \pm 21	50	6831 \pm 759*
	1000	179 \pm 23	100	7336 \pm 674*
	10	180 \pm 20	10	6117 \pm 622
n-hexane	50	196 \pm 21	50	7275 \pm 547*
	100	207 \pm 21*	100	7688 \pm 725*

4. Discussion

Plants are important in finding cure for various human ailments. Inhibition of AA metabolites by natural compounds has previously been reported [33]. Many medicinal plants and their secondary metabolites inhibit both enzymatic pathways of AA, resulting in the simultaneous inhibition of LOX and COX-mediated products [34]. However, natural inhibition of inflammatory products and simultaneous elevation of antioxidant defense activities is not well known. In the current investigation, we report that *Lycopersicon esculentum*, especially its aqueous fraction, strengthens the antioxidant defense system and inhibits COX pathway of AA metabolism.

In the present study crude extract showed partial inhibition of PAF-induced platelet aggregation while significant activities against AA-induced platelet aggregation and COX-mediated production of TXB₂ were observed. It also significantly elevated GPx enzyme activity. This suggests that crude extract contains compounds that are responsible for the inhibition of COX pathway of AA metabolism. Inhibition of TXB₂ and AA-induced platelet aggregation but lack of any significant effect on LOX-mediated AA metabolites indicates that crude extract of *Lycopersicon esculentum* does not have dual inhibitory properties against both COX and LOX as reported previously for some other medicinal plants. Partial effect on PAF and no significant effect on collagen, ADP, 12-HETE and SOD indicate that either crude extract of *Lycopersicon esculentum* lacks compounds affecting these important inflammatory mediators. Another possibility is the presence of inhibitory constituents preventing the action of bioactive compounds against these inflammatory

mediators. The pharmacological actions of aqueous fraction of *Lycopersicon esculentum* were similar to the crude extract with differing only on SOD. This suggests that compounds responsible for the inhibition of AA mediated platelet aggregation and TXB₂ were fully or partially fractionated in the aqueous fraction of *Lycopersicon esculentum*. Crude extract had no significant effect on SOD while aqueous fraction significantly elevated SOD activity. This probably indicates that crude extract contains compounds that prevent SOD elevating actions and these inhibitory constituents were not fractionated into the aqueous fraction. Instead fractionation process de-inhibited the compounds which then enhanced the SOD activity.

Chloroform fraction seemed to be completely devoid of any significant effect on platelet aggregation induced by all four platelet agonists. This means that, like crude extract and aqueous fraction, it possesses no activity against collagen and ADP but unlike crude extract and aqueous fraction, it has no pharmacological action against PAF and AA. Chloroform fraction has very weak action against TXB₂ and hence explaining lack of any significant effect against AA-induced platelet aggregation. Just like crude extract but unlike aqueous fraction, no significant effect was observed on SOD, however, like both crude extract and aqueous fraction, significant effect was observed on GPx. Chloroform fraction significantly inhibited the production of 12-HETE and was the only fraction showing activity against LOX-mediated AA metabolism. This suggests that *Lycopersicon esculentum* possess activity against LOX enzyme but this effect was suppressed in the crude extract. Since no activity of aqueous and n-hexane fractions was observed on

12-HETE, there is possibility that these inhibitors were fractionated to both aqueous and n-hexane fractions. This subsequently de-inhibited the LOX inhibitory compounds in chloroform fraction.

The n-hexane showed most potent inhibitory effect on PAF-induced platelet aggregation compared to partial inhibition by crude extract and aqueous fraction. Furthermore, n-hexane fraction was the only fraction active against human platelet aggregation stimulated by collagen. This indicates that fruit of *Lycopersicon esculentum* does possess compounds active against platelet aggregation stimulated by collagen, and these are only present in the n-hexane fraction. This also indicates the highly polar nature of such compounds. However, just like the crude extract and other fractions, n-hexane showed no effect on platelet aggregation activated by ADP. Furthermore, n-hexane was the only fraction completely devoid of any significant effect against AA metabolism through COX and LOX pathways. This also explains its ineffectiveness against AA-induced platelet aggregation. Just like the aqueous fraction, n-hexane fraction also elevated both SOD and GPx activities. Since GPx enhancing activity was present in the crude extract as well as in all the fractions, this means that multiple compounds are responsible for these effects. The fact that these compounds are distributed throughout various fractions also suggests that these compounds vary in their nature from highly polar to highly nonpolar. Presence of SOD enhancing activities in the aqueous and n-hexane fractions and their relative absence in the crude extract and chloroform fraction indicates that crude extract of *Lycopersicon esculentum* contains suppressor ingredients which upon fractionation are distributed to the chloroform fraction.

Various metabolites produced through the actions of COX and LOX on AA play a key role in the process of inflammation [35]. Therefore, it is likely that fruit of *Lycopersicon esculentum* will have at least, some therapeutic effect in diseases with inflammation as their hallmark [36]. The results of our study demonstrate that anti-inflammatory and cardiovascular effects of *Lycopersicon esculentum* are mediated through multiple pathways. The compounds responsible for these pharmacological actions were however, distributed throughout various fractions of *Lycopersicon esculentum*. Aqueous fraction was mostly active against COX pathway of AA metabolism while chloroform was the only fraction possessing significant activity against LOX pathway. Aqueous and n-hexane fraction seem to have concentrated compounds responsible for elevating SOD activity while n-hexane was the most potent against PAF and the only fraction exhibiting potent activity against collagen induced platelet aggregation. Compounds responsible for elevating GPx activity seems to be distributed throughout various fractions of *Lycopersicon esculentum*.

The main phytochemical constituents of *Lycopersicon esculentum* include flavonoids (kaempferol, quercetin, rutin and naringenin), carotene (lycopene) and other compounds like caffeic, chlorogenic, ferulic and p-coumaric acids [37,38]. These compounds have shown their effects as antioxidant and antiplatelet [39,40] obtained from other plants so there is possibility that the antioxidant and

antiplatelet activities of *Lycopersicon esculentum* may be due the presence of these constituents.

These results not only rationalize the traditional use of *Lycopersicon esculentum* in inflammatory and cardiovascular conditions but also provide a rich source of extracting valuable pure compounds against important inflammatory mediators.

5. Conclusions

The results of this study clearly showed that the aqueous fraction of *Lycopersicon esculentum* was mostly active against cyclooxygenase pathway of AA metabolism while chloroform was the only fraction possessing significant activity against lipoxygenase pathway. Aqueous and n-hexane fraction seem to have concentrated compounds responsible for elevating SOD activity while n-hexane was the most potent against PAF and the only fraction exhibiting potent activity against collagen-induced platelet aggregation. Compounds responsible for elevating GPx activity seems to be distributed throughout various fractions of *Lycopersicon esculentum*. The results of our study demonstrate that anti-inflammatory and cardiovascular effects of *Lycopersicon esculentum* are mediated through multiple pathways.

Authors' Contributions

Sagheer Ahmed, Abdul Waheed Khan and Arif-ullah khan were the principal investigators, brought the idea of experiments and wrote the manuscript. Saima Gul purchased the tomato's fruits, crushed it and made three different fractions of it (i.e. water, n-hexane and chloroform). Kashif Iqbal, Muhammad Usman and Hafsa Bibi collect blood samples from human volunteers and also assist in research activities throughout the project. Mr. Abdul Waheed Khan also revised the whole manuscript and discussed with correspondence author for correction.

Declarations

Ethics Approval and Consent to Participate

The project was approved by the Kohat University of Science and Technology Ethics Committee. The project aim was explained to all participating people to be part of the study, for blood samples to be drawn and to publish results obtain from the study.

Competing Interests

The authors have no any competing interests.

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