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Health Promoting Bioactivities of Fruit Juice of Water Melon (*Citrullus lanatus*) in Rabbits Overdosaged with Panadol Extra Using Liver Biomarkers

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Abstract:

Watermelon juice is commonly used as beverage and to relieve thirst. It contains phytochemicals like alkaloids, flavonoids, saponnins. The fruits are rich in lycopene and with a total antioxidant capacity similar to tomato The fruits are also rich source of β -carotene, vitamins (B, C and E), minerals (K, Mg, Ca and Fe), amino acid (citrulline) and phenolics. This work therefore aimed at determining yhe health promoting bioactivities of fruit juice of water melon (citrullus lanatus) in rabbits overdosaged with panadol extra using liver biomarkers. Thirty rabbits classified into six groups of five rabbits labelled A-F including subgroups identified as C1, C2, E1 and E2 were studied. Toxicity was induced with 1500mg/Kg body weight while reduction in toxicity or protective activities was carried out by administering 15ml/Kg body weight into the rabbit before, after or without the inducement of toxicity. Plasma Alanine Transaminase (ALT), Aspartate Transaminase(AST), Total Bile Acid(TBA) and Albumin used as biomarkers to monitor the procedure were analysed biochemically by spectrophotometry. The result showed a significant increase in ALT, AST and TBA following the administration of

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1500mg/Kg body weight in the experimental rabbits than the control rabbits($p<0.05$). There was also a significant reduction in the elevated plasma ALT,AST and TBA in experimental rabbits as a result of the administration of 1500mg/Kg of Panadol extra after the administration of 15ml/Kg of watermelon juice($p<0.05$). Watermelonjuice has been demonstrated to reduce hepatotoxicity in rabbits overdosaged with Panadol extra.

Key words: Bioactivities, Water Melon Juice, Rabbits, Overdose, Panadol Extra, Liver Biomarkers

INTRODUCTION

1.1 Background to the Study

Watermelon fruit belongs to the family of Cucurbitaceae, in the genus: citrullus, and is related to the other same family members such as cantaloupe, squash, and pumpkin that run as vines on the ground surface. It is widely grown across many tropical countries where it is one of the major commercial fruit crops. Botanical name: is *Citrullus lanatus* [1].

Watermelon comes in several colors, including red, pink, orange and yellow. Watermelons contain more water and less sugar or sodium, besides being excellent sources of vitamins. The red watermelon has lycopene in high quantities. Lycopene is an antioxidant and helps to prevent many diseases [2][3][4]. One(1) cup of watermelon juice (about 150g) contains, 7.5-10mg Lycopene, Beta carotene and lycopene are compounds which guard plants against damage from sunlight[6]. These help to neutralize the "free radicals," roaming molecules that cause tissue and organ damage, in our bodies. Free radicals contribute to inflammation and cholesterol deposits in blood vessels, causing strokes and heart attacks. Lycopene helps to minimize risks of strokes and other ailments like rheumatoid arthritis, osteoarthritis, colon cancer and asthma. Watermelon

is an important addition for a low-fat, low-cholesterol diet [6]. Watermelon is rich in antioxidants that help to prevent kidney stones, cancers and cardiac ailments. Another benefit is that watermelon is a great source of potassium, which helps to regulate blood pressure levels keeping your heart healthy[2][3][4][5]. Watermelon juice is essential as a preventive against bone loss. A watermelon diet is an excellent source of energy because it contains Vitamin B. It can offer more nutrients per calorie as it mainly made of water and contains very few calories[2][3][4]. Watermelon seeds are rich sources of protein and micro and macro-nutrients like calcium, iron, potassium, zinc and phosphorus. Watermelon juice helps to lower risks of age-related macular degeneration that may lead to loss of vision in elders[6].

The fruit is beneficial in checking erectile dysfunction and increases insulin sensitivity. It is full of antioxidants shown to reduce the inflammation that contributes to diabetes, asthma, atherosclerosis, colon cancer, and arthritis. When watermelon is eaten, the Citrulline within watermelon is converted to an amino acid called Arginine[6]. Arginine is great for our heart, liver and circulatory system and helps us to maintain a healthy immune system - making watermelon a heart-healthy food choice. The antioxidants, such as Citrulline in watermelon can reduce toxins in the body. Some of these toxins are believed to trigger asthma attacks. Watermelon is rich in Vitamin C and Beta-Carotenes. Both have anti-inflammatory properties that can help relieve the symptoms of arthritis. Containing 92% water, this melon acts as a natural diuretic that cleanses your kidney and bladder. The cleansing properties of watermelon may also reduce the risk of clogged arteries. The fruit is also believed to increase HDL (good cholesterol levels) [6]. A glass of watermelon juice can naturally eliminate waste and promote proper digestion[6]. Again, the diuretic effect of watermelon can eliminate water retention. It

is especially recommended for women who retain fluids during menstruation or pregnancy. Watermelon contains Folic acid and Citrulline that works in tandem with other essential vitamins. Some research indicates that these vitamins may reduce the risk of a heart attack, stroke and colon cancer [1].As the water from the melon cleanses your system, it can flush out the toxic waste that cause some forms of itchiness. The Lycopene in watermelon has been extensively reported to reduce the risk of prostate cancer. Watermelon can also be used as a beauty aid to reduce skin blemishes. Simply rub your skin with a small piece of watermelon. Leave the juice on for 10 minutes before rinsing [6].

There are several implications of excessive consumption of watermelon. Actually it is the excessive lycopene that causes the problem associated with too much consumption of watermelons; it causes indigestion, gas formation, nausea and vomiting because too much of anything is not good at all. [6].Thus intestinal disturbance is one of the prime reasons of having so many watermelons in a day and especially for elderly people because the intestinal tract is weaker with age and the symptoms are more exaggerated than normal. Watermelons contain high levels of potassium and high potassium levels can lead to complexities of the heart and the nervous system. [1].Too much of potassium can mess with the normal heart beats, weak or absent pulse and can lead to heart attack. It can also lead to damage of kidneys and control of motor nerves [1]. People suffering from the kidney problems must refrain from eating too many watermelons as it can seriously cause internal damage. Some people have allergy to watermelons and eating them can trigger various allergic reactions in the body like rashes, itching, sneezing etc.. Excessive intake of watermelons increase the levels of Nitric Oxide which has a relaxing effect on the body [1].It may also decrease the blood pressure and in many cases this may be harmful as too much decrease in the

blood pressure may cause the internal arteries to be damaged.. Excessive intake of watermelons can cause detrimental effects on the body on organs such as kidneys, nervous system, heart, arteries and nerves[1]. [1]

Panadol Extra is a pain reliever available from pharmacies. It contains two active ingredients — paracetamol and caffeine. Compared with paracetamol alone, Panadol Extra improves pain relief for some people [7]. The caffeine in Panadol Extra can cause anxiety and sleeplessness, but this is very rare when Panadol Extra is used correctly. However, you may be more likely to get these side effects if you consume caffeine-containing food and drinks when taking Panadol Extra. Make sure that you don't take more than eight Panadol Extra caplets in 24 hours (equivalent to four grams of paracetamol)[15]. Many different brands of pain relievers and cold and flu remedies contain paracetamol. Each tablet contains Paracetamol 500 mg and Caffeine 65 mg. Two tablets up to four times daily. The dose should not be repeated more frequently than every 4 hours[15]. Do not exceed 8 tablets in 24 hours and not recommended for children under 12 years. Panadol extra could cause undesirable side effects such as: Thrombocytopenia, Agranulocytosis, Anaphylaxis, Cutaneous hypersensitivity reactions including skin rashes, angioedema and Stevens Johnson syndrome/toxic epidermal necrolysis, Bronchospasm, Nervousness, Dizziness and Hepatic dysfunction[8]. Liver damage is possible in adults who have taken 10 g or more of paracetamol. Ingestion of 5 g or more of paracetamol may lead to liver damage if the patient has risk factors. Symptoms of overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and abdominal pain. Liver damage may become apparent 12 to 48 hours after ingestion[9] Abnormalities of glucose metabolism and metabolic acidosis may occur. In severe poisoning, hepatic failure may progress to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death.

Acute renal failure with acute tubular necrosis, strongly suggested by loin pain, haematuria and proteinuria, may develop even in the absence of severe liver damage. Cardiac arrhythmias and pancreatitis have been reported[8]. Most patients who have taken an overdose of Panadol extra will initially be asymptomatic, as clinical evidence of end-organ toxicity often does not manifest until 24-48 hours after an acute ingestion.. Minimum toxic doses of Panadol extra for a single ingestion, posing significant risk of severe hepatotoxicity, are as follows:: Adults: 7.5-10 g and Children: 150 mg/kg; 200 mg/kg in healthy children aged 1-6 years[8][10].

1.2 Broad Objective

To assess health promoting bioactivities of water melon (*Citrullus lanatus*) fruit juice in rabbits overdosaged with panadol extra.

1.3 Specific objectives

To assess changes in plasma concentration of ALT, AST, TBA, albumin in rabbits treated with water melon (*Citrullus lanatus*) fruit juice following panadol extra overdose.

HYPOTHESES

The following hypothesis will be tested:

H_1: That there will be no significant alteration in liver biomarkers following the administration of 30ml/kg of raw watermelon juice in rabbits after a seven day overdose with panadol extra;

H_2: That there will no significant hepatotoxic effect of 30ml/kg of raw watermelon juice in rabbits administered with the juice compare with normal control rabbits;

H_3: That there will be no significant hepatoprotective effect of watermelon in rabbits overdosaged with Panadol extra

following administration of 60ml of raw watermelon juice for 7 days;

H_4: That there will be no significant effect of Panadol overdose on liver biomarkers in rabbits;

H_5: That there will be no significant effect of simeontaneous administration of 30ml/kg of raw watermelon juice and Panadol extra overdose on liver biomarkers in rabbits.

METHODOLOGY

3.1 Materials

3.1.1 Study area

This study will be carried out in at Achievers University animal house, Owo Local Government area of Ondo state in Nigeria.

3.1.2 Study population

Thirty rabbits will be purchased in Owo through the Department of Biological Sciences, Achievers University, Owo – Nigeria and will be divided into six groups.

3.1.3 Control Group

Group A: 5 rabbits fed with normal meal and water for 7 days (normal control)

3.1.4 Experimental groups

Group B: 5 rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days

Group C: 5 rabbits given 1500mg/kg of panadol extra per oral and thereafter fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days after 5 days of post panadol extra administration

Group D: 5 rabbits given 1500mg/kg of panadol extra per oral and fed with normal meal and water for 7 days

Group E: 5 rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days after which each rabbit was given 1500mg/kg of panadol extra per oral and fed with normal meal and water The rabbits were observed for another 7 days post panadol extra administration.
Group F: 5 rabbits given 1500mg/kg of panadol extra per oral and were simultaneously fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days.

3.1.5 Biological sample

Group A: Five milliliters of blood sample was collected from the 5 rabbits before and after 7 days feeding with normal meal and water (normal control)
Group B: Five milliliters of blood sample was collected into Lithium heparinized bottle from each of the 5 rabbits before and after 7 days normal meal and 30ml/Kg of watermelon juice
Group C:. Five milliliters of blood sample was collected into Lithium heparinized bottle from each of the 5 rabbits after 5 days of post 1500mg/kg of panadol extra administration. Five milliliters of blood sample will be collected into Lithium heparinized bottle from each of the 5 rabbits after 7 days of the administration of 15ml/Kg of watermelon juice daily
Group D: Five milliliters of blood sample was collected into Lithium heparinized bottle from each of the 5 rabbits before and after 7 days of post- administration of 1500mg/kg of panadol extra per oral and fed with normal meal and water.
Group E: Five milliliters of blood sample was collected into Lithium heparinized bottle from each of the 5 rabbits before and after 7 days feeding with normal meal and 15ml/Kg of watermelon juice and administration 1500mg/kg of panadol extra per oral.
Group F: Five milliliters of blood sample was collected into Lithium heparinized bottle from each of the 5 rabbits before and after 7 days of the administration of 1500mg/kg of

panadol extra per oral and with silmeontaneous administration of 15ml/Kg of watermelon juice.

3.2. Methods

3.2.1 Treatment of normal control and experimental rabbits

Group A: 5 rabbits fed with normal meal and water for 7 days (normal control)

Group B: 5 rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days

Group C: 5 rabbits given 1500mg/kg of panadol extra per oral and thereafter fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days after 5 days of post panadol extra administration

Group D: 5 rabbits given 1500mg/kg of panadol extra per oral and fed with normal meal and water for 7 days

Group E: 5 rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days after which each rabbit was given 1500mg/kg of panadol extra per oral and fed with normal meal and water The rabbits were observed for another 7 days post panadol extra administration.

Group F: 5 rabbits given 1500mg/kg of panadol extra per oral and were simultaneously fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days **.**

3.2.2 Preparation of watermelon juice

Water melon was purchased from Owo markets and will be presented to the Department of biological sciences, Achievers University, Owo for confirmation and certification.

The succulent red part was removed and kept in a sterile bowl. The seeds were aseptically removed. The remaining succulent red part of the watermelon will be blend using electric blender and thereafter was filtered undiluted.

Sixty milliliter of the filtrate was then administered to the rabbits as watermelon juice.

3.2.3 Preparation of Panadol extra powder

Panadol extra tablets of GlaxoSmithkline was purchased and grind into powder using Laboratory pestle and mortal.

Blood Sample preparation

Whole blood samples collected from each of the rabbits was collected in Lithium heparinized tubes. The blood sample was spun using bench/macro centrifuge for the extraction of the plasma.

3.2.4 Estimation of Liver biomarkers

Aspartate Aminotransferases (AST) assay

The aminotransferases are a group of enzymes that catalyse the inter conversions of amino acids and a-oxoacids by transfer of amino groups. AST (aspartate aminotransferase or glutamate oxaloacetate transaminase) has been found in the cytoplasm and the mitochondria of cells. In cases of mild tissue damage e.g. liver the predominant form of serum AST is that from the cytoplasm, with a smaller amount coming from the mitochondria. Severe tissue damage will result in more mitochondrial enzyme being released. Elevated levels of AST can signal myocardial infarction, hepatic disease, muscular dystrophy and organ damage[11].

Principle: Colorimetric method (Reitman and Frankel) for determination of serum aspartate aminotransferase. Aspartate Aminotransferase is measured by monitoring the concentration of oxaloacetate hydrazone formed with 2, 4-dinitrophenyl-hydrazine.

Alanine Aminotransferases (ALT) assay

ALT belongs to a group of enzymes called aminotransferases. The enzyme ALT been found to be in highest concentrations in the liver, with decreasing concentrations found in the kidneys, heart, skeletal muscle, pancreas, spleen and lung tissue respectively. ALT measurements are used in the diagnosis and treatment of certain liver diseases (e.g. viral hepatitis and cirrhosis) and heart diseases.

It is often tested in combination with AST as part of a liver panel with ALT levels being higher in most types of liver disease[11].

Principle: Alanine aminotransferase (ALT) catalyzes the transamination of L-alanine to α-ketoglutarate (α-KG), forming L-glutamate and pyruvate. The pyruvate formed is reduced to lactate by lactate dehydrogenase (LDH) with simultaneous oxidation of reduced nicotinamide-adenine dinucleotide (NADH). The change in absorbance is directly proportional to the ALT activity and is measured using a bichromatic (340, 700 nm) rate technique.

Plasma Albumin assay

Patients who have chronic liver disease and kidney disorders are at risk of developing abnormal Albumin concentrations in the blood. Albumin has special relevance to patients with diabetes because its presence in urine is a marker of diabetic kidney disease. The Albumin test allows for timely and accurate assessment of kidney disease; resulting in the correct adjustment of treatment and accurate monitoring of the complications of diabetes[11].

Principle: The measurement of serum albumin is based on its quantitative binding to the indicator 3,3',5,5'-tetrabromo-m cresol sulphonephthalein (bromocresol green, BCG). The

albumin-BCG-complex absorbs maximally at 578 nm, the absorbance being directly proportional to the concentration of albumin in the sample.

Total Bile Acids

Bile is a complex mixture of lipids, protein, carbohydrates, mineral salts, vitamins, and various trace elements, with bile acids making up about 67% of the total composition. Bile acids are produced from excess cholesterol, secreted from the liver, absorbed into the small intestines, and returned to the liver with portal blood. While bile acid synthesis is critical for the removal of cholesterol from the body, bile acids are also needed for proper uptake of dietary lipids, fat soluble vitamins, and other nutrients into the small intestines. Under physiological conditions, newly synthesized bile acids are conjugated to glycine or taurine to form bile salts, and not much free bile acid is actually found in bile [11].

Principle of assay

Cell Biolabs' Total Bile Acid Assay Kit measures the total bile acid within serum, plasma, and cell or tissue lysate samples. The assay is based on an enzyme driven reaction: when bile acids are incubated in the presence of 3α-hydroxysteroid dehydrogenase (3α-HSD), NADH, and thio-NAD+, thio-NAD+ is converted to its reduced form Thio-NADH. Thio-NADH is then detected colorimetrically as an absorbance increase at 405 nm .

3.2.5 Method of data analysis

The results will be subjected to statistical analysis using SPSS to determine the level of significance of differences at 0.05 level of significance using students' 't' test.

RESULT

Table 4. 1: The mean and standard deviation of ALT,AST, Albumin and TBA obtained in the rabbits

	GRPA	GRPB	GRPC1	GRPC2	GRPD	GRPE1	GRPE2	GRPF
ALT/UL10-40 IU/	25±3.0	22.1 ±2.1	61±1.5	31±2.5	60±2.0	24±2.0	32±2.1	36±2.0
AST/UL	34±1.5	31±3.0	67±2.0	39±2.2	67±1.0	33±2.0	41±2.0	47±1.6
TBA/ µmole/L	6±1.0	5±0.5	16±2.0	7±1.5	17±1.0	6±1.2	7±1.0	6±0.5
Albumin/ g/dl	3.8±0.5	3.6±0.5	3.0±0.3	3.6±0.2	3.1±0.1	3.5±0.5	3.2±0.2	3.5±0.4

Group A: 5 rabbits fed with normal meal and water for 7 days (normal control)

Group B: 5 rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days

Group C: 5 rabbits given 1500mg/kg of panadol extra per oral, fed with normal meal, observed for 5 days and thereafter administered with 15ml/Kg of watermelon juice daily for 7 days after 5 days of post panadol extra administration

Group D: 5 rabbits given 1500mg/kg of panadol extra per oral and fed with normal meal and water for 7 days

Group E: 5 rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days after which each rabbit was given 1500mg/kg of panadol extra per oral and fed with normal meal and water The rabbits were observed for another 7 days post panadol extra administration.

Group F: 5 rabbits given 1500mg/kg of panadol extra per oral and were simultaneously fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days.

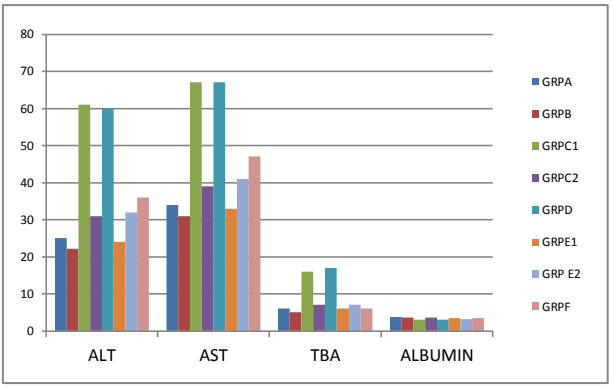

Figure 4.1: The value of ALT, AST, Albumin and TBA obtained in the rabbits

Table 4. 2: The comparative analysis of ALT,AST, Albumin and TBA obtained in the rabbits

		A Vs B	A Vs D	C1 Vs C2	E1 Vs E2	A Vs F
ALT/UL10-40 IU/	**"t"**	0.83	-9.71	10.61	-2.83	-3.05
	"P"	0.25	0.005	0.0044	0.053	0.046
	Comment	p> 0.05*	p< 0.05**	p< 0.05**	p> 0.05*	p< 0.05**
AST/UL	**"t"**	0.95.	-23.34	9.90 .	-2.83 .	-9.19
	"P"	0.22	0.001	0.005	0.053	0.006
	Comment	p> 0.05*	p< 0.05**	p< 0.05**	p> 0.05*	p< 0.05**
TBA/ µmole/L	**"t"**	0.89	-7.78.	3.18. .	-0.71 .	-10.59
	"P"	0.23	0.008	0.043	0.28	0.0044
	Comment	p> 0.05*	p< 0.05**	p< 0.05**	p> 0.05*	p< 0.05**
Albumin/ g/dl	**"t"**	0.28	1.37.	-1.66	0.56 .	0.47
	"P"	0.40	0.15	0.12	0.32	0.34
	Comment	p> 0.05*	p> 0.05*	p> 0.05*	p> 0.05*	p> 0.05*

The result obtained showed no significance difference in the mean value of ALT, AST, TBA and Albumin in rabbits fed with normal meal and water for 7 days (normal control)compared with rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days (P>0.05) (tables 1&2 and figure 1). There was no significant difference in the mean values of plasma albumin in the comparative analysis of all the groups(p>0.05) (tables 1&2 and figure 1). There was a significantly lower difference in the mean value of ALT, ASTand TBA in rabbits

fed with normal meal and water for 7 days (normal control)compared with rabbits given 1500mg/kg of panadol extra per oral and fed with normal meal and water for 7 days and rabbits given 1500mg/kg of panadol extra per oral and were simultaneously fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days ($p<0.05$). (tables 1&2 and figure 1). There was also a significantly lower mean plasma value of rabbits administered with 15ml/Kg of watermelon juice daily for 7 days after 5 days of post panadol extra administration than when the rabbits were given 1500mg/kg of panadol extra per oral and normal meal and observed for 5days ($p<0.05$).However there was no significant difference in the mean value of 5 rabbits fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days compared with when the rabbits were given 1500mg/kg of panadol extra per oral post – administration of 15ml/Kg of watermelon juice daily for 7 days ($p>0.05$) (tables 1&2 and figure 1).

5. DISCUSSION, CONCLUSION AND RECOMMEDATION

5.1 Discussion

The significantly lower difference in the mean value of ALT, AST and TBA in rabbits fed with normal meal and water for 7 days (normal control)compared with rabbits given 1500mg/kg of panadol extra per oral and fed with normal meal and water for 7 days and rabbits given 1500mg/kg of panadol extra per oral and were simultaneously fed with normal meal and 15ml/Kg of watermelon juice daily for 7 days could be attributed to hepatotoxicity effect of Panadol extra especially the acetaminophen content which could cause liver dysfunction and damage. In addition the watermelon juice taken together with Panadol extra overdose could not prevent the magnitude of the toxicity[12].

There was also a significantly lower mean plasma value of rabbits administered with 15ml/Kg of watermelon juice daily for 7 days after 5 days of post panadol extra administration than when the rabbits were given 1500mg/kg of panadol extra per oral and normal meal and observed for 5days.

This finding could be associated with the possible hepatotoxicity reduction effect of watermelon juice due to the phytochemical constituents such as lycopene, flavonoids, Beta carotene and saponins which are potent antioxidants that prevents cellular damage. In this study rabbits treated with water melon juice showed possible reduction in Panadol extra toxicity which could be responsible for the decrease in ALT,AST and TBA as against the result obtained in Panadol extra toxicity[13][14].

1. The significant reduction in the plasma ALT, AST and TBA in the rabbits after toxicity and increase in the activities and concentration of the parameters could be attributed to the fact that liver metabolize bile acids hence a good index of liver disorder [11] and ALT and AST are liver enzymes that leak into the blood circulation hence the increase due to Panadol extra toxicity which was decreased by watermelon juice due to potent antioxidants[11][13][14].

5.2 Conclusion

Watermelon juice has been demonstrated to reduce Panadol extra hepatotoxicity considering the significant alterations in the plasma values of ALT, AST and TBA.

5.3 Recommendation

Further research could be carried out on the dosage appropriation of water melon juice to treat hepatotoxicity in humans.

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