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## Introduction:

Hyperuricemia (High Uric Acid) is an excess of uric acid in the blood, as a plasma uric acid concentration  $>6.8$  mg/dl (Choi *et al.*, 2005). It is

closely linked with hypertension and cardiovascular disease. Most of asymptomatic hyperuricemia may cause gout or Peripheral neuropathy through crystal-independent pathways (**Chizyński and Rózycka 2005 and Sam et al., 2010**).

Aspirin (acetylsalicylic acid) is a Non Steroidal anti-Inflammatory Drug (NSAIDs) are used on a large scale as anti-inflammatory, reduce fever and analgesic. Aspirin has a wide range of therapeutic activities such as prevent further heart attacks, arthritis disease and prevention of blood clots (**Al Janabi et al., 2005 and Tashsp 2011**). Its side effect includes liver dysfunction, stomach ulcers, GIT bleeding, tinnitus and hyperuricemia (**Brayfield 2014**). Aspirin In low dosages (60–300 mg once daily), aspirin reduces uric acid excretion, and may induce hyperuricemia, whereas higher doses are uricosuric( **Gershon SL, Fox,1994** ). This paradoxical effect of salicylate can be explained by two modes of salicylate interaction with the urate monocarboxylate exchanger (URAT1): acting as an exchange substrate to facilitate urate reabsorption at low dose, and acting as an inhibitor for urate reabsorption at high dose (**Caspi et al., 2000**).

*Annona muricata* (Linn.) is a tropical fruit belongs to family *Annonaceae*, commonly known as soursop or graviola (**Badrie and Schauss 2009**). It is one of Medicinal plants worldwide that studied in the last decades due to its therapeutic potential. The no botanical studies have indicated that *A. muricata* has been used as parasiticide (**Moghadamtousi et al., 2015**), insecticide (**Hanaa, 2014** ).

The fruit is used as natural medicine for neuralgia (**Oberlies et al., 1997**). Diarrhea anti-malaria (**Badrie and Schauss, 2009**) and arthritic pain (**Boakye et al., 2015**). Fruit juice and infusions of leaves used to protect against fainting and treat fever (**Leboeuf et al., 1980**). In last years it has become widely used for hypoglycemic (**Hanaa, 2014**), useful in cancer treatment (**Mishra et al., 2013**), liver and kidney diseases (**De Sousa et al., 2010**).

*Annona muricata* have been reported to contain highly bioactive compounds such as murihexocin , annocuricin and annohexocin (**Hasrat et al., 1997**). It is considered as a source of annonaceous acetogenin compounds (AGEs) that has high potency and effectiveness against lipid

oxidation and free radicals, with wide scope of pharmacological and phytochemical effect for human body (**Hamizah et al., 2012**).

*Annona muricata*, commonly known as soursop fruit, has long been used as a natural remedy for a variety of illnesses and subject of countless medicinal uses. The bark and leaves of the soursop tree was confirmed to contain antioxidant, insecticide, antipyretic, antidiabetic, antihypertensive and antibacterial activities (**Kedari, Khan, 2014; De Sousa et al., 2010**). Recent studies revealed that the extracts obtained from various parts of the soursop plant possess antioxidant, anti-lipidemic (**Kumaret al., 2015; Tomar et al., 2012**). Anti-oxidant and anti-hyperuricemia activity on rats (**Sunarni et al., 2015; Wahjuni et al., 2012**).

The granule produced from the juice of soursop fruit proved effective to decrease uric acid level in both oxonate-induced male and female rats. The possible mode of action of the granule might be related to high polyphenolic compounds and vitamin C or the presence of uricase-like compounds in the soursop fruit. Further, soursop granule can be produced commercially to substitute the use of allopurinol (**Prasetyorini Djarot, 2018**).

The aim of the present study was to evaluate the effect of some different levels of *Annona* juice as source of natural antioxidants on the side effects of aspirin induced hyperuricemia in rats.

## Materials and methods:

### Materials :

**Annona** (*Annona muricata L.*): were purchased from a local market in Zagazig (Egypt).

The basal diet was prepared according to **Reeves et al., (1993)** the recommended dietary allowances

**Aspirin Drugs:** (*Acetylsalicylate acid* <sup>®</sup>): Aspirin 75mg/tablet for Pharmaceutical and Chemical Industries, Cairo, Egypt.

### Experimental animals:

Thirty five adult male albino rats of Sprague Dawley strain weighing 130± 10g were purchased from the Animal House in the Institute of Ophthalmology, Giza, Egypt.

## Methods:

**Preparation of juice:** Whole fresh fruits were sorted, (1 kg of annona, about 5) was the method of (**Peckhan and Gladys 1974**). Employed in the drink preparation but with some modifications. For biological experiment, the juice was concentrated to one fifth the volume by lyophilization then aliquots were kept frozen at  $-20^{\circ}\text{C}$  until used according to (**Gyamfi et al., 2011**).

## Proximate analysis:

Moisture content, crude protein, crude fiber, crude fat and ash of **annona** were determined according to (**A.A.C.C. 2000**). Moreover, carbohydrates were calculated by difference. Antioxidant activity% was determined according to (**A.O.A.C. 2007**). Phenolic compounds were determined by HPLC according to the method of (**Goupy et al., 1999**).

## Experimental rats design:

Rats were kept under observation for one week for adaptation and fed on basal diet (BD). 7 rats served as negative control group and ٢٨ rats were received oral aspirin 3.5 g/ kg body for one week by stomach tube to induce hyperuricemia according to

**Caspi et al., 2000** and reclassified into control positive group and 4 treated rat groups that treated with 100,200 and 300 grams of Annona juice respectively. Food and water were provided ad-libitum. Food intake was recorded daily and body weight of rats was measured once weekly according to **Chapman et al., (1950)**. At the end of the experimental period (six weeks), the rats were anaesthetized by diethyl ether and sacrificed. Blood samples of each rat were withdrawn in test tube to coagulation then centrifuged at 3000 rpm for 15 minutes to obtain serum for estimation of some biochemical analysis

## Biochemical analysis:

Serum uric acid, creatinine and urea were determined according to the method of (**Fossati et al., 1980; Bartles, 1972 and Patton and Crouch, 1977**). Serum alanine, (ALT and AST), and ALP enzymes activity and serum total bilirubin were estimated according to (**Reitman and Frankel, 1957, Kind and King, 1954 and Dumas et al., 1973**). Total antioxidants capacity (TAC), superoxide dismutase (SOD) activity, and

malondialdehyde (MDA) were determined according to (Nishikimi *et al.*, 1972, Cao *et al.*, 1993 and Ohkawa *et al.*, 1979), respectively.

### Statistical Analysis:

Results are expressed as the mean standard deviation SD. Data were statistically analyzed of variance “ANOVA” test at  $P \leq 0.05$ ) according to **Snedecor and Cochran, (1967)**, using SPSS statistical software, version 13.0 was used for these calculations.

### Results and discussion:

*Annona (Annona muricata L.)* fresh fruit was analyzed to obtain its chemical composition and results were illustrated in table (1). The amount of moisture, ash, protein, fiber, fat and carbohydrates of *Annona* juice are (73.28, 0.5, 1.22, 1.82, 0.24 and 22.56 w/w) respectively. These results are agreed with the findings of **Champy *et al.*, (2005)** who found that, the amounts of protein, fat, ash, fiber and carbohydrates of whole fresh *Annona* fruit were (1.54, 0.26, 0.58, 1.148 and 25.19 g/100g), respectively.

**Table (1): Chemical composition of *Annona* (mg/100gm fresh weight basais)**

Element	Composition (mg/100gm)
Moisture	73.28
Protein	1.22
Fat	0.24
Ash	0.5
Dietary fiber	1.82
Carbohydrate	22.56

Values are the means of 3 independent determinations.

Chemical analysis of *Annona* fruit was carried out to determine the antioxidant activity % and Total phenols (mg/100g) content and the results were representing in Table (2). It is clearly shown that antioxidant activity of *Annona* fruit is 92.53% while its total phenol is (4261.38 mg/100 gm). Accordingly, this result was highly matched with **Ghana *et al.* (2019)** who found that the total phenolic content of *Annona* fruit pulp determined from the phosphor molybdenum assay to be 49.03 gAAE/100 g. **Hanaa (2014)** reported that the total phenolic of essential oils of *Annona* leaf is 50.88 gAAE/100 , she also stated that the most of the total phenolic compounds were found in the *Annona* fruit pulp and leaf but the

leaf essential oil has better scavenger of the DPPH radical than the fruit pulp essential oil.

**Table (2): Total phenolic content (mg/100g) and antioxidant activity radical % of Annona juice**

Parameters	content
Total phenolic content (mg/100g)	4261.38
Antioxidant activity (%)	92.53

The main effect of Annona juice at different concentrations on body weight gain, food intake and food efficiency ratio (FER) of experimental rats are presented in Table (3). The results showed that weight gain of negative control group was 140.2g/day while it was 102.8g/day in positive control group which treated with oral Aspirin. On other hand, the weight gain of groups treated with Annona juice 100ml/kg, 200ml/kg and 300ml/kg are (131, 129.8 and 125 g/day) respectively. As shown, there is a significant decrease in mean value of body weight gain of positive control group compared to negative control group. rats treated with Annona juice showed a significant increase in mean value of body weight gain in compare to positive control group treated with aspirin.

**Table (3): Body weight gain (g), feed intake (g/day) and feed efficiency ratio (FER) of negative control and hyperuricemia rat groups**

Parameters Groups	Weight gain (g/day)	Feed intake (g/day)	FER %
Group 1: Control (-ve)	140.2±7.08a	15.66±0.78a	0.077±0.51a
Group 2: Control (+ve)	102.8±8.73b	13.48±1.16b	0.058 ±0.45b
Group 3	131.0±3.39a	15.17±0.94a	0.077±0.18a
Group 4	129.8±3.37a	15.28±0.72a	0.77±0.23a
Group 5	125.0±6.44a	15.36±0.83a	0.076±0.33a

**Values in each column which have different letters are significantly different (p<0.05).**

Positive control group showed decrease in mean value ± SD of feed intake and FER compared to negative control group. While treating with Annona juice at different concentrations showed a significant increase in mean value ± SD of food intake and FER in compare to positive control group. Treating with Annona juice showed non-significant effect in

compare to negative control group. This result is matched with **Sørensen et al., (2000)** who reported that Aspirin is medically used as analgesic, anti-platelets and anti-inflammatory drug which sometimes lead to unexplained weight loss due to gastrointestinal bleeding and stomach upset especially in high doses or long run treatment.

Phytochemical studies of Annona fruit showed much improvement in keeping the general health in good condition, annona contains essential oils like  $\delta$ -cadinene, epi- $\alpha$ -cadinol and  $\alpha$ -cadinol which playing a great role in elimination of free radicals and prevention the formation of the initiator radical appetite (**Kossouh 2007**).

**Table (4): Some liver and renal function parameters of negative control and hyperuricemia rat groups at the end of the study**

Parameters Groups	Uric acid (mg/dl)	Urea (mg/dl)	Creatinine (mg/dl)	AST ( $\mu$ /ml)	ALT ( $\mu$ /ml)	ALP ( $\mu$ /ml)	Bilirubin ( $\mu$ /ml)
Group 1: Control (-ve-)	2.48 $\pm$ 0.31c	18.21 $\pm$ 1.23d	0.78 $\pm$ 0.16c	21.13 $\pm$ 5.57d	29.10 $\pm$ 3.51d	2.73 $\pm$ 0.37c	0.58 $\pm$ 0.07c
Group 2: Control (+ve)	5.94 $\pm$ 0.56a	34.87 $\pm$ 3.05a	2.94 $\pm$ 0.56a	30.00 $\pm$ 3.32a	43.07 $\pm$ 6.82a	4.09 $\pm$ 0.53a	1.77 $\pm$ 0.24a
Group 3	3.92 $\pm$ 0.43b	24.53 $\pm$ 3.99b	2.01 $\pm$ 0.26bc	25.02 $\pm$ 4.30b	34.41 $\pm$ 4.93b	3.80 $\pm$ 0.25b	1.39 $\pm$ 0.04b
Group 4	3.04 $\pm$ 0.40b	20.07 $\pm$ 3.40c	1.21 $\pm$ 0.22b	22.61 $\pm$ 3.51bc	30.83 $\pm$ 6.46c	2.94 $\pm$ 0.24bc	0.98 $\pm$ 0.03c
Group 5	2.76 $\pm$ 0.41b	19.83 $\pm$ 4.03d	0.83 $\pm$ 0.14bc	21.50 $\pm$ 3.35c	29.64 $\pm$ 6.02 cd	2.81 $\pm$ 0.33c	0.63 $\pm$ 0.04c

**Values in each column which have different letters are significantly different ( $p < 0.05$ ).**

Results in Table 4 representing mean values of liver enzymes profile and kidney enzymes profile of experimental rat groups. Oral intake of aspirin (3.5 g/Kg/bw/rats) produced significant increase in serum uric acid, urea, creatinine, bilirubin, AST, ALT and ALP levels in compare to negative control group. Rats treated by Annona juice with different concentrations showed significant decrease in serum uric acid, urea, creatinine, bilirubin, AST , ALT and ALP levels in comparing to positive control group. Treating with annona juice (300 g/Kg/bw/rats) had the best results between the others concentrations, it reversed the toxic effect of aspirin. This result was agreed with other researchers **Watson et al., (2001)**.



Arachidonic acid (AA) is an essential fatty acid belongs to omega 6 family. It is vital to the operation of the prostaglandin system which plays a role in metabolic activities, inflammation, blood pressure, platelet aggregation and vasoconstriction/dilation ( **Smith et al., 2011**).

Aspirin inhibits the ability of kidney to excrete uric acid and causes hyperuricemia via inhibition of prostaglandin synthesis by cox 1 and cox 2 inhibitions in kidney that can leads to hemodynamic acute kidney injury that may result in fatty liver disease and acute encephalopathy ( **Wallace 2008**).

the chemical composition of the Annona fruit consisted largely of terpenes and terpenoids, it contains  $\alpha$ -cardinol,  $\tau$ -cadinol and octadecane that make it a good candidate to treat liver and heart diseases in folk medicine ( **Moghadamtousi et al., 2015**). There was a significant matching between our study and the results of **Kossouh et al., (2007)** he claimed that Annona contains  $\beta$ -caryophyllene in high concentration which shows highly protective effects agninst neuro- degenerative disease and protect liver and kidney from oxygen-derived from free radicals.

**Arthur et al., (2012)** found that that Annona muricata extract has a great role in bilirubin levels reduction, as the extract contains glucosides that might be converted into glucuronic acid which can conjugate with bilirubin for excretion. The extract of Annona muricata reversed the hepatotoxicity-induced Acetaminophen ( **Nwokocha et al., 2012**). In vitro study, it has been found that flavonoids isolated from Annona squamosa L. against hyperuricemic experimental rats via inhibition of xanthine oxidase enzyme compared to allopurinol which make it possible to be used as anti-gout agent to treat high uric acid ( **Mieke Alvionita, 2019**).

**Table (5): Some antioxidant parameters of negative control and hyperuricemia rat groups at the end of the study**

Parameters Groups	Total antioxidants (mmol/L)	Superoxide dismutase (U/mL)	Malondialdehyde (mmol/L)
Group 1: Control (- ve-)	2.56± 0.75 a	162.23± 12.74 a	4.67± 0.76 c
Group 2: Control (+ve)	1.28± 0.55 c	114.33± 12.01 d	10.05± 1.16 a
Group 3	1.79±	137.12±	7.2±



	0.65 b	13.01 c	0.86 b
Group 4	1.99± 0.80 b	153.33± 14.81b	5.01± 0.62 c
Group 5	2.01± 0.09 b	156.01± 12.10 b	4.81± 0.32 c

**Values in each column which have different letters are significantly different ( $p < 0.05$ ).**

Data in Table (5) presented the effect of Annona juice treatment on total antioxidants, Superoxide dismutase and MDA of rats. Total antioxidants and superoxide dismutase levels of aspirin treated rats were decreased while there was a significant increase of MDA level compared with negative control group. Rats treated with different concentrations of Annona juice increased significantly the Total antioxidants and superoxide dismutase while hepatic MDA level was decreased in compare to positive control group. Furthermore, various studies demonstrated that the mechanism of action of antioxidant compounds from *A. muricata* is by hydrogen donation as it is mainly lipophilic compounds (Ishola *et al.*, 2014).

For instance (Baskar *et al.*, 2007) has discovered that *A. muricata* contains antioxidant compounds such as phenols and flavonoids that restores the activity of enzymes such as glutathione (GHS), nitric oxide (NO), superoxide dismutase (SOD), prostaglandin E2 (PGE-2) and malondialdehyde (MDA). *A. muricata*'s ethanolic extract reversed lipid peroxidation that caused by cold of the immobilization stress in the brain and liver of rats (Padma *et al.*, 2001).

## Conclusion

It could be concluded that, the administration of *Annona muricata* juice at different concentrations possesses significant anti-uricemic and antioxidant activities which could protect against hyperuricemia-induced aspirin in experimental rats due to its highly rich in remarkable amount of total phenolics and flavonoid components.

## Abstract:

Effects of different this stud designed to investigate the phytochemicals contents and biological concentrations of *Annona* juice with the objective of inhibition or decreasing uric acid production in

hyperuricemia-induced aspirin. Thirty-five adult male albino rats Sprague Dawley strain weighting ( $130\pm 10g$ ) were randomly classified into five groups (7 rats each). The first group served as a negative control group, fed on basal diet only. The other four groups were fed on basal diet and received oral aspirin 3.5 g/ kg body for one weeks to induce hyperuricemia and reclassified into positive control (untreated) and treated rat groups that were 100,200 and 300 grams of Annona juice respectively. The treatment period is designed for six weeks. The chemical composition of Annona juice showed higher value of Moisture and carbohydrate but lower value of Fat, Ash, Protein and fiber. The Antioxidant activity and Total phenolic higher percent in Annona juice. In compared to positive control group, the treated rats group with Annona juice showed a significant increase in weight gain, food intake and FER and also Total antioxidants and Superoxide dismutase but a significant decrease in serum Uric acid, Urea, Creatinine, ALT &AST, ALP, total bilirubin and, MDA at  $P < 0.01$ . Our study clearly demonstrated that administration of an Annona juice alleviates the harmful effect aspirin induced hyperuricemia in rats

**Key words:** Annona muricata; Aspirin; Hyperuricemia; Bioactive compound; Anti-inflammatory , rats

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## التأثيرات الحيوية لعصير القشطة على الآثار الجانبية لزيادة حمض اليوريك في الدم من تناول الأسبرين في فئران التجارب

### ملخص البحث:

ثمره القشطة معروفة باسم القشديات ولها تاريخ طويل في الطب الشعبي في الشرق الأقصى. ويهدف هذا البحث الي دراسة محتويات عصير القشطة من المواد الكيميائية النباتية وتأثيراتها البيولوجية بتركيزات مختلفة لخفض مستوي حمض اليوريك في الدم الناتج من تناول الأسبرين في الفئران ، حيث أجري البحث على خمسة وثلاثون ذكور الفئران من نوع ألبينو سلالة سبراغ داولي تتراوح اوزنهم بين ( ١٣٠ ± ١٠ جم) وقُسمت عشوائياً إلى خمس مجموعات "سبع فئران في كل مجموعة" المجموعة الأولى هي المجموعة الضابطة السالبة حيث تغذت على الوجبة الأساسية فقط. وباقي المجموعات الاربعة تم تغذيتهم على الوجبة الأساسية مع تناول الأسبرين عن طريق الفم بواسطة الانبوبة المعدية بنسبة ٣.٥ جم / كجم من وزن الجسم لمدة اسبوع للإصابة بزيادة حمض يوريك في الدم وإعادة تقسيمهم إلى المجموعة الضابطة الايجابية (غير معالجة) ومجموعات الفئران المعالجة والتي تناولت عصير القشطة بنسب ٣٠٠ جرام على التوالي. وكانت فترة العلاج لمدة ستة. أسابيع وأظهرت نتائج التركيب الكيميائي لعصير القشطة ٢٠٠، ١٠٠، والكربوهيدرات والرماد والبروتين والألياف وأعلي قيمة في نشاط مضادات الأكسدة ونسبة الفينول الكلية. كما محتواه من الرطوبة والدهون اسفرت النتائج البيوكيميائية وذلك بالمقارنة مع المجموعة الضابطة الإيجابية إن مجموعات الفئران المصابة والمتناولة لعصير القشطة أظهرت زيادة معنوية في زيادة الوزن وتناول الطعام و نسبة كفاءة الغذاء "FER" ومضادات الأكسدة الكلية وانزيم السوبر اكسيد ديسموتاز بينما اظهرت انخفاض معنوي في حمض اليوريك في الدم ، اليوريا ، الكرياتينين ، ALT & AST ، ALP ، البيليروبين الكلي و MDA عند  $P < 0.01$ . وأظهرت دراستنا بوضوح أن تناول عصير القشطة يخفف من التأثير الضار الذي يسببه الأسبرين في ارتفاع مستوي الدم من حمض يوريك في الفئران

**الكلمات الأساسية:** ثمره القشطة، أسبرين، ارتفاع حمض اليوريك في الدم، المركبات الحيوية المضادة للالتهاب. فئران التجارب.