IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 2 Ser. 10 (February. 2019), PP 33-42
www.iosrjournals.org

Tachyphylaxis Demonstrated In The Effect Of Capsicum Annum On Gastric Acid Secretion.

Dr. Nndunno Akwaras[1], Christian Onahinon[2] Dr. Emmanuel Eru[2], Dr Julie Ibu[3] , Dr Adugba Augustine[2], Prof. John Ibu[2] .

[1](Senior Registrar, Family Medicine Department. Federal Medical Centre, Makurdi, Nigeria).
[2](Department of Physiology, College of Health Sciences, Benue State University, Makurdi, Nigeria).
[3](Chief Inspector, National Youth Service Corps, Benue State Secretariat Makurdi, Nigeria).
Corresponding Author: Dr. Nndunno Akwaras

***Abstract**: Capsicum annum is one of the species of peppers that are used as culinary spices. The effect of edible substances on gastric acid secretion has been of interest but not much has been studied on Capsicums (peppers). This prompted the present study. Wistar rats weighing between 200-300 g were randomly placed in five groups having 8 rats per group and received aqueous extract of Capsicum annum. Doses of 10%, 20%, and 30% of LD_{50} and supramaximal doses of 10mg, 20mg, 30mg, 40mg, 50mg, 60mg, 70mg and 80mg of the aqueous extract were administered through a gastric fistula and 10 minutes aliquot samples collected over 120 minutes. Gastric acid secretion was measured by titrating the aliquots to phenolphthalein end point. The result of gastric acid secretion in mmol/L/hour was, basal acid output (BAO) 15.6 ± 0.19. 10% LD_{50} were 17.52 ± 0.03, 18.30 ± 0.03, 18.84 ±0.04, 19.20 ± 0.05, 19.08 ±0.07, 17.58 ± 0.16, 13.14 ± 0.24, 8.4 ± 0.16, 7.02 ± 0.13 at 40, 50, 60, 70, 80, 90, 100, 110, 120 minutes respectively. Results showed a rise between 50 and 90 minutes followed by decline between 90 and 120 minutes. This decline indicates that Capsicum annum demonstrates tachyphylaxis.*

***Key Words**- Gastric acid secretion, Capsicum annum, Tachyphylaxis.*

Date of Submission: 03-02-2019 Date of acceptance: 18-02-2019

I. Introduction

Capsicum annum is a specie of peppers and contains capsaicin which is responsible for its burning sensation. There are other capsaicinoids in peppers such as dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin and homocapsaicin. Capsaicin is a transient receptor potential vanilloid agonist (TRPV1) [1] TRPV1 is also receptive to other endovanilloids, heat ($>46^{o}$ C) and acidosis (pH <6) [2, 3]. TRP channels are important in acid sensing. Acid sensing is important for maintainance of pH homeostasis of the stomach. The activity of TRPV1 is controlled by a multitude of regulatory mechanisms that either cause sensitization or desensitization of the channel [3]. Capsaicin is highly selective and highly potent at this channel [4].

Patterns of gastric acid secretion have been implicated in many gastrointestinal diseases and since peppers are widely consumed, it is important to assess its effect on gastric acid secretion. Holzer has drawn attention to the challenge of understanding the physiological and pharmacological implication of TRPV1 agonist, antagonist, uncompetitive inhibitors, drugs that interfere with TRPVI sensitization, drugs interfering with intracellular trafficking of TRPV1 and TRPVI agonists for local administration [3].

II. Materials And Methods

2.1 *CAPSICUM ANNUM* (PEPPER)

Capsicum annum fruits were bought from the local market (Wadata Market) in Makurdi, Benue State, Nigeria. The pepper (Fig 1) was identified by a taxonomist in the department of Botany, Faculty of Sciences of Benue State University, Nigeria and a specimen voucher deposited in their herbarium.

FIGURE 1- Specimen of *capsicum annum* fruit.

2.2 DRUGS AND CHEMICALS

Analytical grade Sodium hydroxide (NaOH), Sodium Chloride (NaCl) and phenolphthalein made by May and Baker (Dagenham, England) and urethrane made by Sigma Chemical Co. (Poole, UK).

2.3 ANIMALS

Forty Albino Wistar rats weighing 200-300g of both sexes were obtained from the animal house of the College of Health Sciences, Benue State University, Makurdi and nursed under the same conditions in the animal house research laboratory. They were subjected to a 12 hour light and dark photic cycle, fed on normal rat chow (Pfizer Limited, Kaduna, Nigeria) and given water ad libitum. Permission for the use of the animals was obtained from the Animal Ethics Committee of Benue State University Makurdi, Nigeria.

2.4 PREPARATION OF THE EXTRACT

The aqueous extract preparation was modified following the method of Alnaqeeb *et al*., [5]. 50g (Wt 1) of the fresh fruit was thoroughly washed and placed in clean beakers (Pyrex, 500 ml). It was homogenized in 75ml (V1) of cold sterile 0.9 % saline in the presence of some crushed ice using an electric blender. The homogenous mixture was filtered with Whatman no1 filter paper and centrifuged at 2000 rev/min for 10 minutes and the clear supernatant was collected and volume noted (V2). The volume of the wet residue was noted as Wt 2. The volume of the supernatant was subtracted from the volume of the cold saline used in homogenization (V1 – V2) or V3 which was noted as Wt 3. The yield of each of the three preparations was used to determine the stock concentration:

stock concentration = Wt1 - (Wt2 + Wt3) ÷ V2……..(1)

[yield = Wt1 - (Wt2 - Wt3)]…….(2)

The above formula was used to calculate the stock concentration of each which was then stored in refrigerator until used. The required amount was administered in mg / 100 gram body weight of each animal.

50 g of *Capsicum annum* contains 0.001 ± 0.00 g of capsaicin [6]. Oral LD_{50} values of Capsaicin are 161.2 mg / kg (16.12 mg / 100 g body weight) and 148.1 mg / kg (14.81 mg / 100 g body weight) for male and female rats respectively [7].

The above information from literature was used to determine the dose of capsicum extract that will be administered.

2.5 ANIMAL GROUPING AND EXPERIMENTAL DESIGN

40 Wistar rats weighing between 200 - 300 grams were randomly assigned to five groups consisting of 8 each as follows:

Group 1- Control group for *Capsicum annum* which were administered normal saline.

Group 2- were administered 10% LD_{50} of *Capsicum annum.*
Group 3- were administered 20% LD_{50} of *Capsicum annum*.
Group 4- Control group for successive supramaximal doses of *Capsicum annum* which were administered normal saline.
Group 5 - were administered successive supramaximal doses of *Capsicum annum* of 10mg, 20mg, 30mg, 40mg, 50mg, 60mg, 70 mg and 80mg.

2.6 SURGICAL PROCEDURE

After a 12 hour fast, each animal was anaesthesized with 25 % Ethyl Carbonate (urethane) at a dose of 0.6 ml/100 g body weight intraperitoneally.

Tracheostomy was performed. A nasogastric tube was passed. A duodenostomy was performed and normal saline was used as gastric lavage to wash out the debris from the stomach until clear effluent was obtained. A duodenogastric canula was passed and ligated insitu for subsequent collection of gastric acid secretion. 10 minutes aliquot samples were collected from the duodenal canula. A gastric fistula was created in the fundus with insertion of a 2 way canula to allow the administration of the extract. The aliquots were each titrated to a phenolphthalein end point using 0.01M NaOH and the acid output or concentration is calculated as described by Ibu [8,9] :

Where Normality = Molarity

MA x VA = MB x VB……(3)

MA = (MB x VB) ÷ VA…… (4)

Where,

MB = Molarity of base known (0.01N) = 10mMol

VB = Volume of base known (titrate of NaOH) used

VA = Volume of acid (effluent volume) = 10ml

Substituting for MB and VA

MA = 10 x VB ÷ 10…… (5)

Therefore MA=VB ……(6)

Acid output / 10 minutes = VB mMol / L / 10 mins……..(7)

Acid output per hour = VB x 6 mMol/ L / hour as stated by Ibu [10]…….(8)

The results were analysed for graphics and statistics using SPSS version 22. Statistical differences were accepted at 95% Confidence level when P <0.05.

III. Result

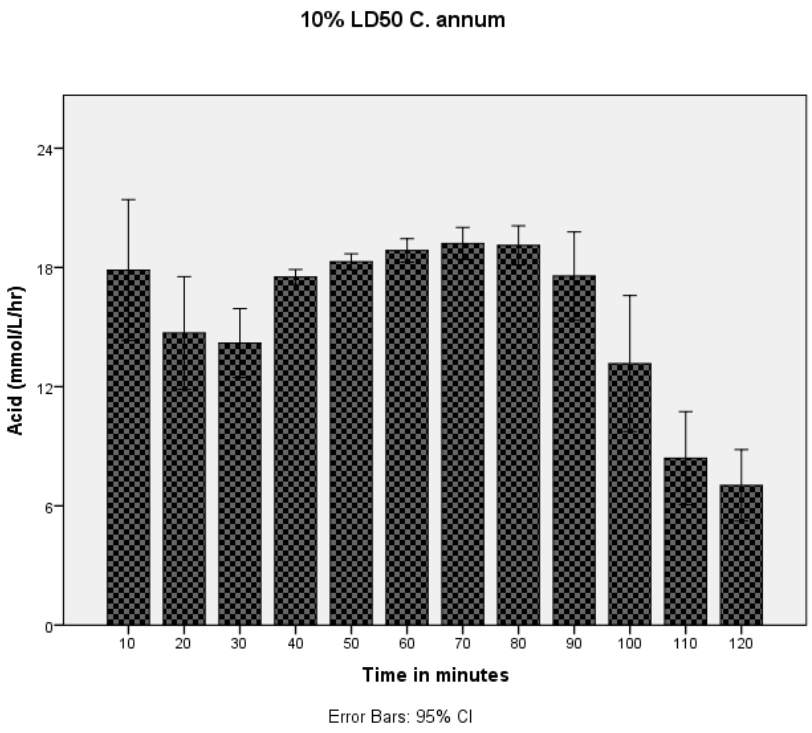

Figure 1- shows graph of administration of 10 % LD_{50} of *Capsicum annum* extract.

The acid produced increased steadily until it reached a plateau between 70 and 80 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis

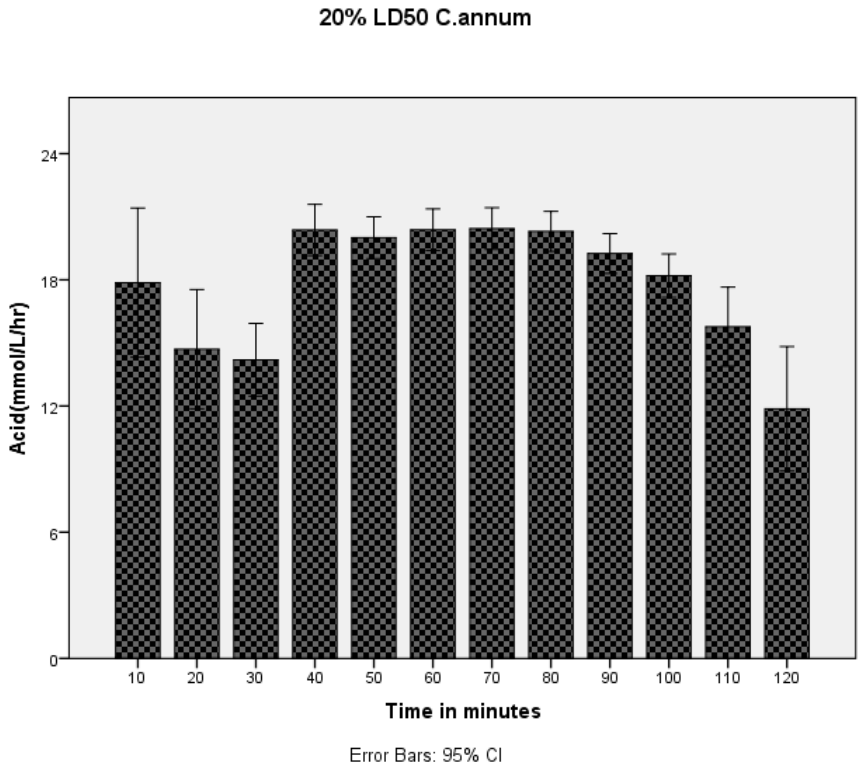

Figure 2- shows graph of administration of 20 % LD $_{50}$ of *Capsicum annum extract*

The acid produced increased steadily until it reached a plateau between 40 and 80 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis.

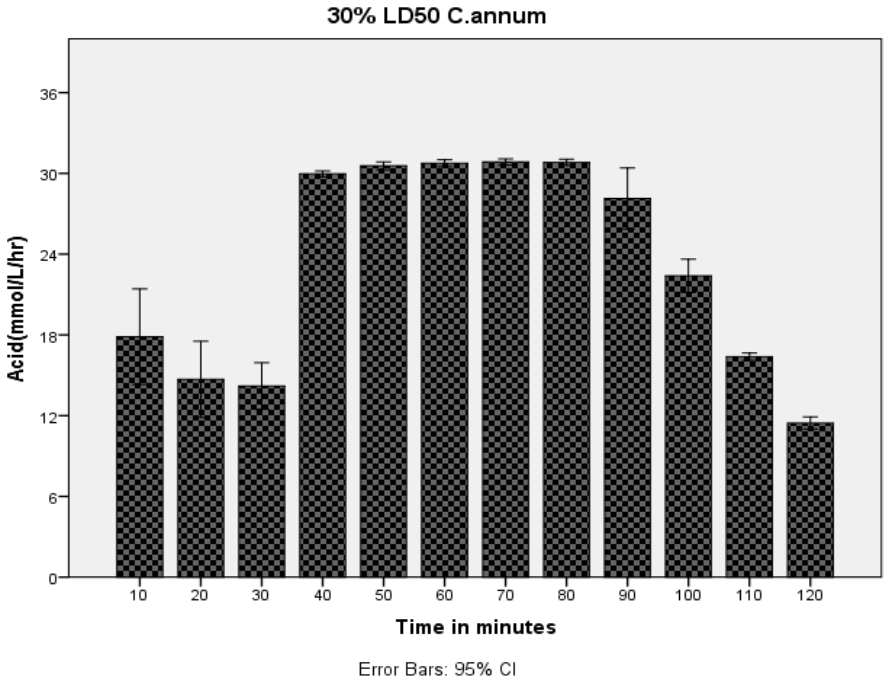

Figure 3- shows graph of administration of 30 % LD $_{50}$ of *Capsicum annum* extract.

The acid produced increased steadily until it reached a plateau between 40 and 80 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis

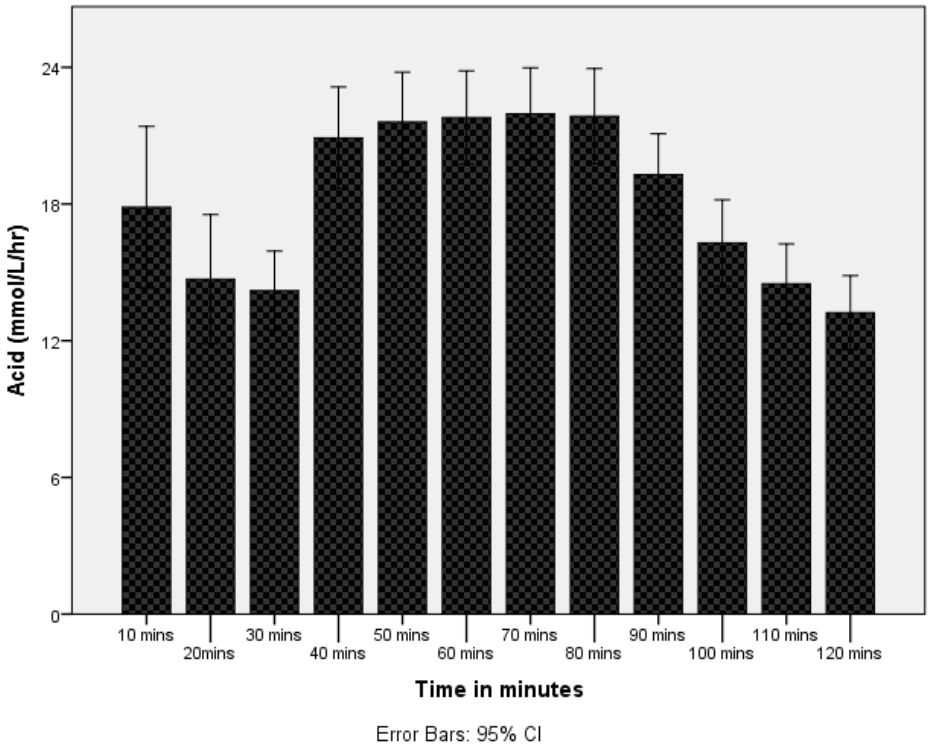

Figure 4- shows graph of administration of 10mg of *Capsicum annum* extract.

The acid produced increased steadily until it reached a plateau between 40 and 80 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis.

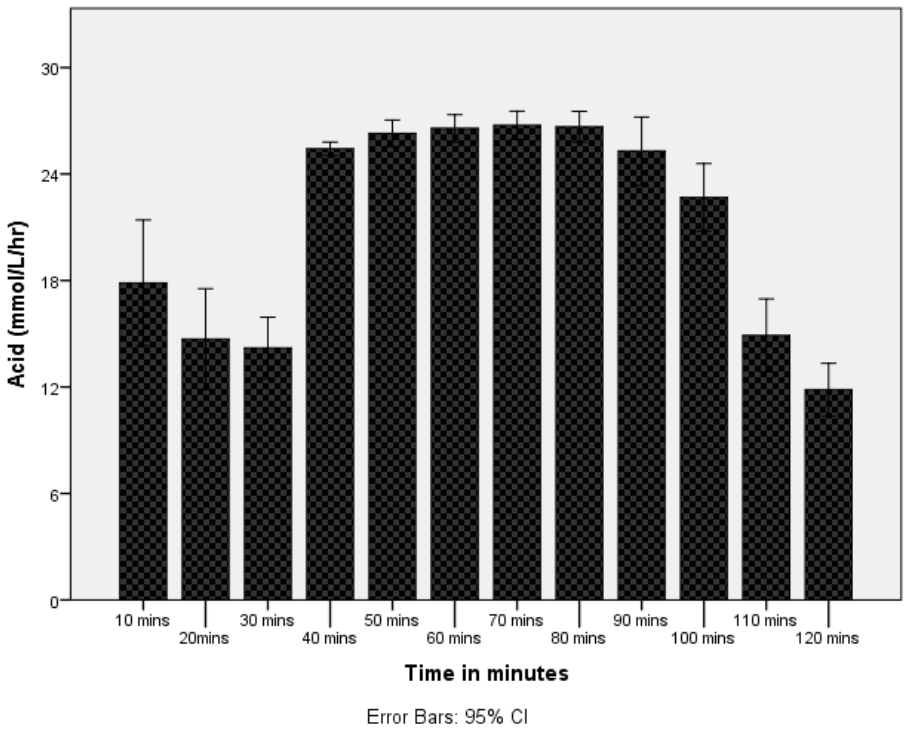

Figure 5- shows graph of administration of 20mg of *Capsicum annum* extract.

The acid produced increased steadily until it reached a plateau between 40 and 90 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis.

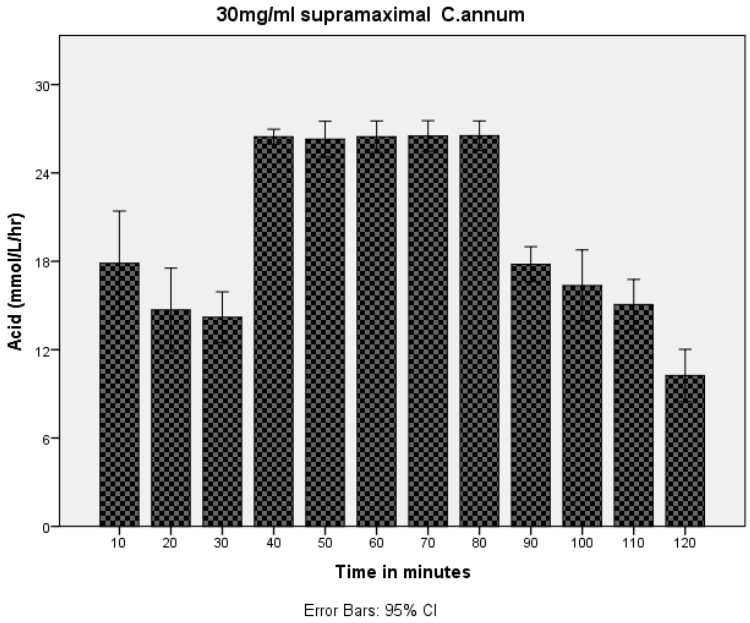

Figure 6- shows graph of administration of 30mg of *Capsicum annum* extract.

The acid produced increased steadily until it reached a plateau between 40 and 80 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis

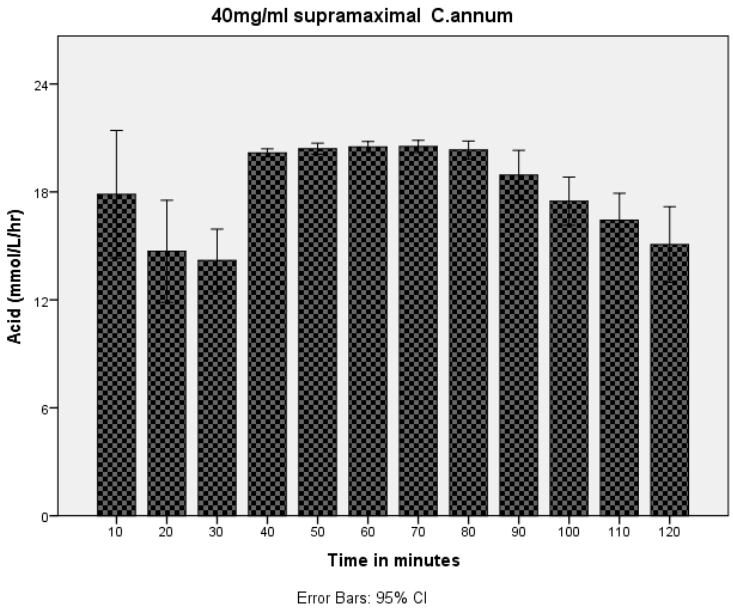

Figure 7- shows graph of administration of 40mg of *Capsicum annum* extract.

The acid produced increased steadily until it reached a plateau between 40 and 80 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis.

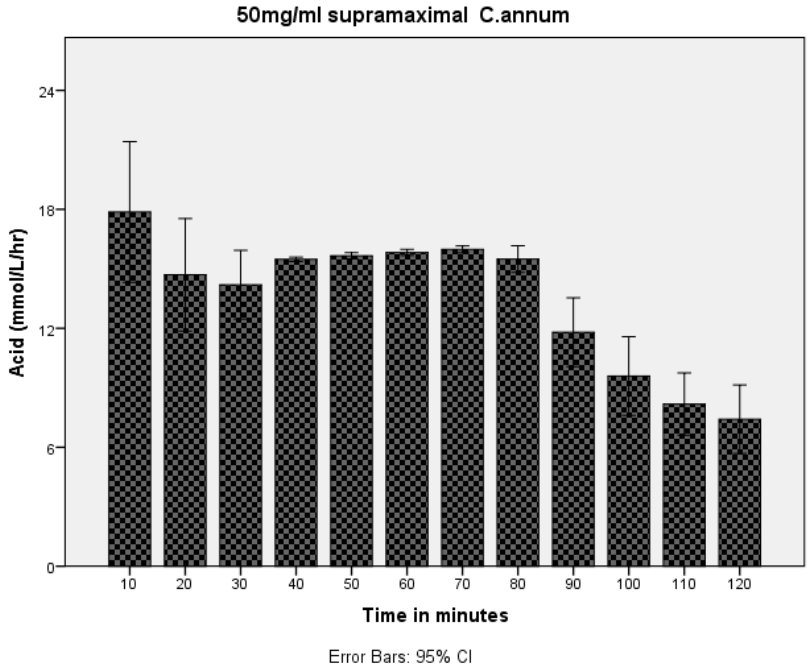

Figure 8- shows graph of administration of 50mg of *Capsicum annum* extract.

Peak acid secretory response was seen at 10 minutes. The acid produced plateaued between 40 and 90 minutes exhibiting saturation phenomenon. After that acid secretory response decreased between 100 and 120 minutes depicting tachyphylaxis.

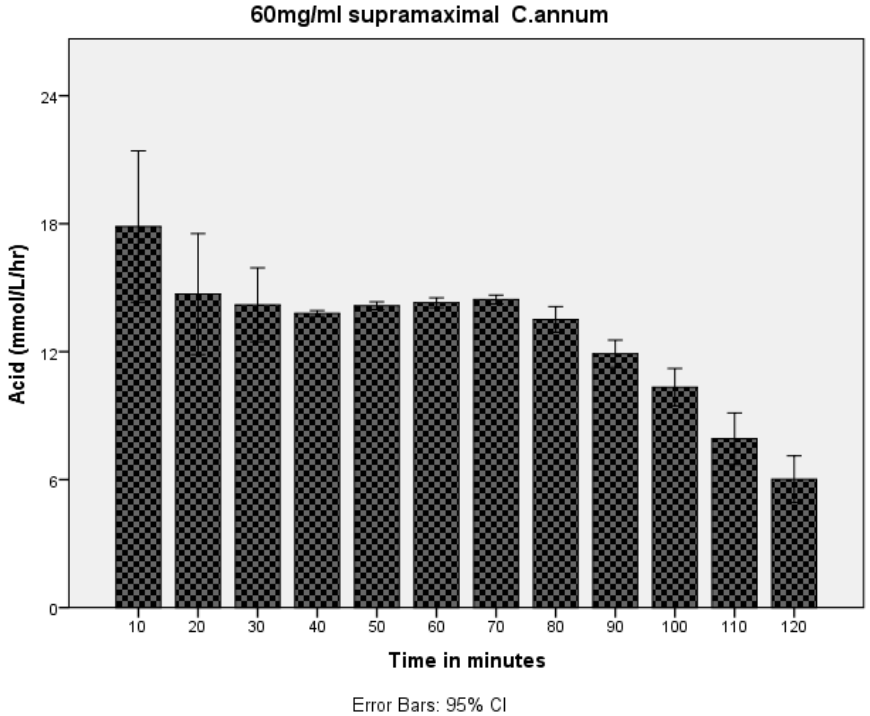

Figure 9- shows graph of administration of 60mg of *Capsicum annum* extract.

Acid output at peaked at 10 minutes thereafter the acid output reached a plateau between 50 and 70 minutes and showed clear decline from 100 to 120 minutes depicting tachyphylaxis.

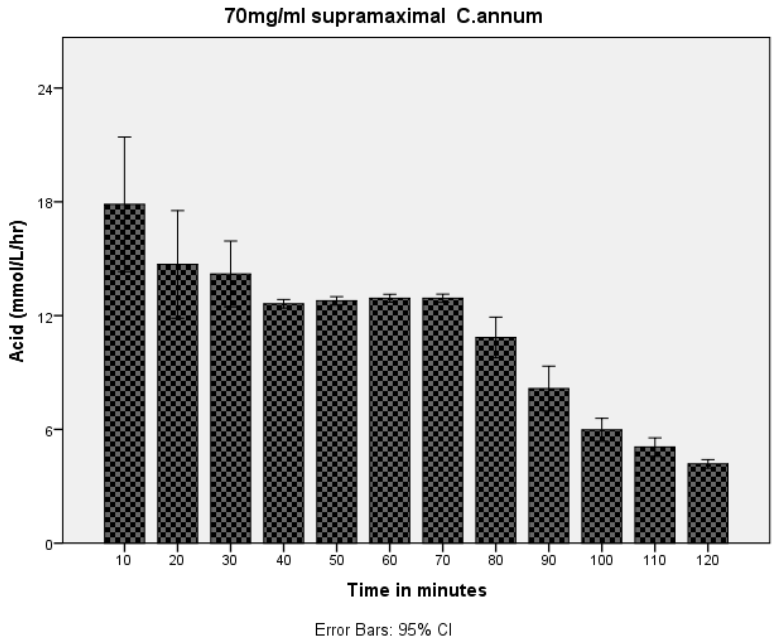

Figure 10- shows graph of administration of 70mg of *Capsicum annum* extract.

Acid output was same between 40 and 70 minutes thereafter the acid output showed clear decline from 90 to 120 minutes depicting tachyphylaxis.

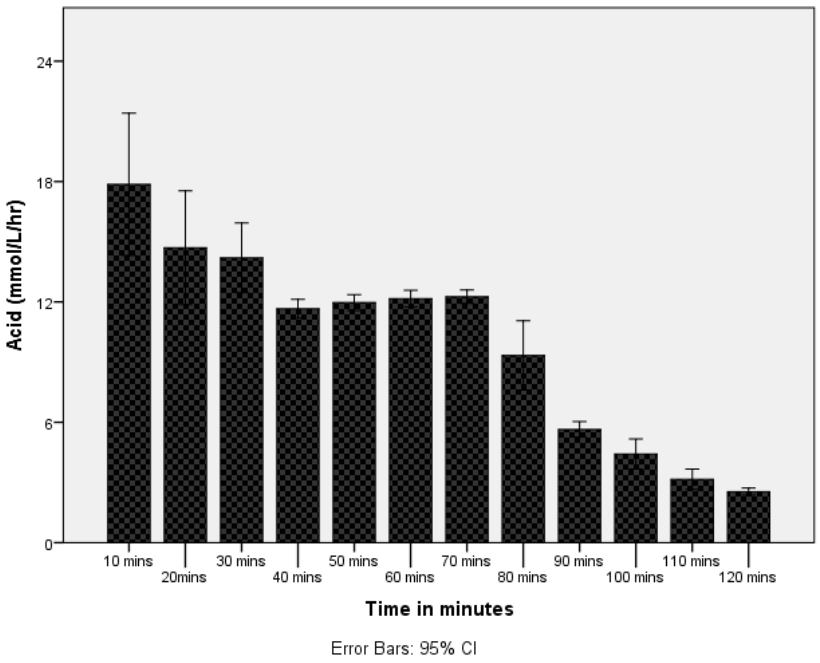

Figure 11- shows graph of administration of 80mg of *Capsicum annum* extract.

Basal acid output at 10 minutes was the highest thereafter the acid output remained low and showed clear decline from 90 to 120 minutes depicting tachyphylaxis

IV. Discussion

The present study show that aqueous extract of Capsicum annum increased gastric acid secretion from 50 minutes to 90 minutes post stimulation thereafter there was persistent and gradual decline in gastric acid secretion between 90 and 120 minutes. This decline is referred to as tachyphylaxis. The physiological explanation for this tachyphylaxis is that capsaicin contained in capsicums activates capsaicin-sensitive afferent neurons [11] and are important in the neuronal mechanism of the stomach and in gastric acid secretion. Peppers have been reported to have conflicting influence on gastric acid secretion. Some studies report that low-dose capsaicin can decrease gastric acid secretion while high-dose increase gastric acid secretion [9,12,13]. The observed decline in the present study may be explained from studies on TRPV1 which is a nonselective cationic channel, which serves as the binding site of capsaicin [14]. A mechanism of initial sensitization, followed by desensitization of gastric norciceptive C-fibers, has been suggested [15]. Also Imatake *et al*., [16] reported that capsaicin inhibited gastric acid output, and the mechanism underlying this effect appears to involve vagal nerve inactivation. Winter, [17] however described two ways by which capsaicin desensitizes nociceptive neurons. These are pharmacological desensitization, where a prolonged and repeated application leads to progressive reduction in the size of subsequent response to capsaicin and the "functional desensitization," where capsaicin leads to a reduction or loss of responsiveness of neurons to other stimuli. Mozsik, stated that Four response stages of capsaicin-sensitive primary afferents exist to capsaicin, depending on the dose and duration of exposure to the drug. These are excitation, a sensory blocking effect, long-term selective neurotoxic impairment, and irreversible cell destruction. The possible roles of four stages of capsaicin-sensitive primary afferents can be evaluated in relation to gastric acid secretion, and to the details of the defensive side of gastric mucosa against different chemicals, physical agents, drugs and other pathological stress [18] Capsaicin in high doses causes functional desensitization. In this study all doses administered over 120 minutes eventually caused a decline in gastric acid secretion implying that apart from dose, the duration of exposure of the capsaicin sensitive nerve to capsaicin affects its function.

Capsaicin has been found to affect calcium:sodium permeability[19,20]. They stated that there is a massive influx of calcium ions down the electrochemical gradient. In addition, there is also release of calcium through the TRPV1 channels activated on intracellular organelles like the endoplasmic reticulum. The excess intracellular calcium triggers calcium-dependent protease enzymes causing cytoskeletal breakdown. Microtubule depolymerization causes a halt in fast axonal transport. [19,20]. Osmotic swelling is caused by the chloride influx. A TRPV1-independent mechanism also exists by causing direct inhibition of electron chain transport and subsequent mitochondrial dysfunction [21]. Thus, multiple mechanisms ultimately lead to loss of cellular integrity and defunctionalization of the nociceptor fibers. The nerve fibers retract to a depth at which mitochondrial function is preserved. Immunohistochemical studies have shown that capsaicin produces highly localized loss of nerve fibers in the epidermis and dermis [22].

It is concluded that tachyphylaxis is exhibited by *Capsicum annum* stimulated gastric acid secretion in albino wistar rats. The tachypylaxis shown in this study may explain why people who take peppers in their diet repeatedly and at high doses eventually end up not having the expected increased acid secretory response.

V. Conclusion And Recommendations

5.1 The results of the present study may be helpful to pharmaceutical manufacturing companies when they are doing their national formulary for the populace.

a. Health education to give public awareness related to the findings in this research will be of importance for pepper consuming persons.

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