Anti-ulcerative Potentials of Turmeric (Curcuma longa) Extract on Gastric Ulcer Induced by Alcohol, Potash and Their Combination in Wistar Rats

ADEBO AUGUSTINA OFURE [a*], AMA-IRUOBE PRECIOUS IRUEBAFA [b], ERHABOR AISOSA PRINCE [c*], OGBETA TAYE SUNDAY [d]

[a] augustinaofure389@gmail.com

[c] erhaboraisosa147@gmail.com

[a] Faculty of Basic Medical Sciences, Human Physiology Department, C.M, Ambrose Alli University, Ekpoma, Edo State, Nigeria. 310103.

[b] Faculty of Basic Medical Sciences, Human Physiology Department, C.M, Ambrose Alli University, Ekpoma, Edo State, Nigeria. 310103.

[c] Faculty of Physical Sciences / Education, Chemistry Department, University of Benin, P.M.B 1154, Benin, Edo State, Nigeria. 300213.

[d] Faculty of Education, CIT (Integrated Sciences) Department, University of Benin, P.M.B 1154, Benin, Edo State, Nigeria. 300213.

Abstract

This study evaluated the anti-ulcerative potentials of Turmeric *(Curcuma longa)* extract on gastric ulcer induced by alcohol, potash and their combination. The study was an experimental study using Wistar rats as a model. We used thirty adult Wistar rats for the experimentation and were assigned into five groups, namely A1, A2, B, C, and D and each group had 6 animals each. Group A1 and A2 were the positive controls for alcohol and potash induced ulcers respectively while groups B, C, and D, served as the test groups, where ulcer was induced using alcohol, potash and their combination respectively, and subsequently treated with turmeric extract. Following induction of gastric ulcer, treatment using turmeric extract was administered 3 hours later and this continued for one week. The results showed reduced mean ulcer scores in the test groups (B= 1.25±0.01, C= 1.30±0.85, D= 2.03±0.11) compared to control (A1= 3.09±00.0, A2= 2.07±0.22) while mean percentage inhibition rate in the treated groups (B= 4.32+00.48, C= 1.09+00.01, D= 2.01+00.66) was lower compared to control (A1= 5.04±00.12 and A2= 2.08±01.00). Although the differences were not statistically significant ($p < 0.05$), they however revealed, in this study, an anti-ulcer attribute to the phytochemicals of turmeric extract. Further studies on this extract are strongly suggested.

Keywords: Turmeric, Gastric ulcer, Phytochemical, Alcohol, Potash, Curcumin

1 Introduction

Gastric ulcer is an important health problem affecting a large number of the population worldwide. In spite of extensive research, it still remains as an important cause of morbidity (Ak and Gülçin, 2008). Given its frequency and difficulties, it is a primary focus for the development of novel therapeutic approaches. One could think of peptic ulcer as a complex disease. Factors including elevated stress, weakened mucosal resistance, hereditary characteristics, and Helicobacter pylori infection, and anti-inflammatory drugs including nonsteroidal anti- inflammatory drugs (NSAIDs) can damage gastric mucosa (Anthwal et *al.*, 2014). NSAIDs and other anti-inflammatory medications are a major, known cause of stomach ulcers and ulcer perforations, gastric, and duodenal bleeding and in ulcer death (Basnet and Skalko-Basnet, 2011). The discovery of highly selective COX-2 inhibitors, which have a lower incidence of stomach mucosal injury, was revolutionary, but soon retracted many of them due to serious cardiovascular adverse events (Gulcubuk *et al.,* 2013).

This study chose turmeric (Curcuma longa), a plant from the Zingiberaceae family, to investigate its anti-ulcer properties, which are known for their potent anti-inflammatory effects (Chong et al., 2014). Considering the morbidity caused by dyspepsia and peptic ulcer disease worldwide, affordable, readily available treatments with fewer side effects are always desirable, especially for those living in less developed and developing nations (Bar-Sela *et al.*, 2010). Turmeric has a prominent place and is considered auspicious in all religious observations in many Indian households. Rhizomes of turmeric are an integral part of the Indian diet used as a flavoring and coloring agent

(Douglass and Clouatre, 2015). The status of turmeric is Generally Recognized as Safe (GRAS). Certain compounds have this classification from the US Food and Drug Administration (FDA), indicating that experts deem their usage as food additives safe for human health. (FDA 2024).

Novel chemical compounds possessing medicinal promise are primarily derived from plants. It is reasonable to consider using plants that have been traditionally used as anti-inflammatory and pain relievers as a useful research tool while searching for new anti-inflammatory and analgesic drugs (Joshi, A., Lehene, S., et al. 2023; Domper Arnal, Hijos-Mallada, and Lanas 2022; Shen et al. 2018; Tian et al. 2019; Zhao et al. 2018; Al-Sayed and Abdel-Daim 2018). In the Indian system of medicine, C. longa has a prominent position and is the focus of much investigation due to its potential medical benefits. Indian medicine uses it to treat wounds, bruises, leech bites, diabetes, edema, anorexia, and sporadic fever. It serves as a germicidal as well. It is also used in traditional medicine for flatulence, dyspepsia, and other gastric problems (Kandiannan *et al*., 2008). Ulcers are sores on the stomach or duodenum's mucous membrane that are defined by a loss of mucosal integrity together with superficial tissue loss. There is a local defect with active inflammation (Huang *et al.,* 2015). Peptic ulcer is considered as one of most common diseases in man leading to human sufferings affecting nearly 5% of the global population. It is called a peptic ulcer because pepsin and hydrochloric acid cause aggravation in most cases. Usual course of the peptic ulcer is characterized by many cycles of healing, relapses and occasional complications (Douglass and Clouatre, 2015). The main contributing component to the pathophysiology of peptic ulcers is imbalances between protecting and destructive agents. Pepsin, acid, H. pylori infection, bile acids, impaired mobility, NSAIDs, corticosteroids, nicotine, etc., are some of the damaging factors while protective factors include prostaglandins, mucus, epidermal growth factors, intact microcirculation, epithelial renewal, alkaline tide, nitrous oxide, phospholipids, and bicarbonate (Jayaprakasha et *al*., 2006). Since peptic ulcer is a major health problem, having alternative therapeutic modalities with lesser adverse effects and diverse favorable biological properties will be beneficial in its management. Therefore, findings from this study will help contribute to local contents on the use of available plant materials in the management of gastric ulcer.

Increased gastrin secretion and acid output with defective gastric emptying mechanism predisposes to gastric ulcer. Lower postprandial pepsin secretion, raised serum PG2 and low PGI/PG2 ratios are considered as risk factors for developing a peptic ulcer (Hussein et al., 2016). In hypomotility at the antropyloric region, there is an increased chance for reflex of duodenal contents into the stomach which can cause chronic inflammation and ulceration. Reactive oxygen species (ROS), acid reflux bile, cytokines like tumor necrosis factors, and external substances like Helicobacter pylori, NSAIDs, alcohol abuse, emotional stress, and smoking can damage gastric mucosa leading to a gastric ulcer (Gulcubuk et *al*., 2013). Mucus bicarbonate barrier, prostaglandins mucosal blood flow, cell renewal and migration, and antioxidants, growth factors all act as gastroprotective factors preventing the gastric mucosal injury. Gastric mucosal barrier will block the back diffusion of (H+). NSAIDs can disrupt this barrier, and H+ can damage it resulting in mucosal injury (Huang et *al.*, 2015). The mucus-bicarbonate layer is the first line of defense because it acts as a physicochemical barrier to many chemicals, including hydrogen ions. The second line of defense is provided by surface epithelial cells for a number of reasons, such as mucus generation and epithelial cell ionic transporters that maintain intracellular pH and bicarbonate production, and intercellular tight junctions (Fiala, 2015). Certain mediators are crucial to the process of cytoprotection. There is a thin layer of alkalinity between the mucus and the epithelial surface because bicarbonate, which is produced by the surface epithelial cells, diffuses up from the mucosa to collect beneath the mucous layer (Hussein *et al*., 2016). Epithelial cells also secrete mucus, which forms a gel that covers the mucosal surface and physically protects the mucosa (Parvathy *et al*., 2009). In Nigeria, stomach ulcers are still among the conditions that are most common. The multiple etiologies to the disease have only contributed to making the case worse. However, there is no concrete cure to gastric ulcer and available drugs which are expensive are only used for management purposes. There is therefore no gainsaying the importance of further evaluations of easily sourced plant material in the management of gastric ulcerations.

Various studies have demonstrated that the extract of C. longa has anti-ulcer, anti-H. pylori, antioxidant, and anti-inflammatory properties. There are some conflicting reports showing its ulcerogenic potential also (Fiala, 2015). Anti-inflammatory drugs such as NSAIDs and glucocorticoids are deleterious to gastric mucosa and can cause peptic ulcer and gastritis. Extract of C. longa which already found to have anti-inflammatory actions if found to have anti-ulcer activity, it will be beneficial in the management of peptic ulcer and related disorders and also can be used as anti-

inflammatory agents with gastroprotective action (Kasinski et *al*., 2008). This study was designed to ascertain the anti-ulcer potential of turmeric (*Curcuma* longa) extract on gastric ulcer. This is to ascertain if there will be reduction in ulcer scores induced by various substances such as alcohol and potash. The study further evaluates turmeric (*Curcuma* longa) extract as a curative substance for alcohol and potash induced gastric ulcers in Wistar rats.

2. Materials and Methods

2.1. Study Design

This study was an experimental study using Wistar rats as a model.

2.2. Materials

The following were used for this study, electronic blender, electronic weighing scale (camry, china. Model: EHA251), surgical kit, absolute ethanol (99.5% w/w 99.7% v/v by JHD Gunsgdong Guanghua chemical factory co. ltd. Shatou, Guangzhou, China), syringes, 10% Formalin, plain bottles, chloroform, and turmeric (*Curcuma longa*).

2.3. Experimental Animal

Thirty adults female Wistar rats, with comparable weights ranging from 70g to 80g were procured from the animal farm of the college of medicine, Ambrose Alli University, Ekpoma, Nigeria. They were moved to the site of the experiment at physiology laboratory II, Department of Physiology, College of Medicine, Ambrose Alli University, Ekpoma, where they were allowed 2 weeks of acclimatization given rat chow (Grower pellets produced by Grand Cereals Ltd, a subsidiary of UAO Nigeria PLC, Jos, Plateau state, Nigeria was obtained from an open shop in Ekpoma, Edo state-Nigeria) and drinking water ad libitum. They were housed in well-ventilated labeled plastic cages (60x35x30) at the site of the experiment. The cages were designed to secure the animals properly especially from direct sunlight, insects and were cleaned daily.

2.4. Animals Grouping

The animals were assigned into five groups of 6 rats each as followed;

Group A1: Animals in this group served as positive controls, and ulcer was induced with alcohol without treatment (positive control group 1).

Group A2: Animals in this group served as positive controls, and ulcer was induced with potash without treatment (positive control group 2).

Group B: Animals in this group were induced with ulcer using alcohol and treated with aqueous turmeric extract (test group 1).

Group C: Animals in this group were induced with ulcer using potash and treated with aqueous turmeric extract (test group 2).

Group D: Animals in this group were induced with ulcer using alcohol and potash and treated with aqueous turmeric extract (test group 3)

2.5 Experimental procedures

2.5.1 Preparation of aqueous turmeric extract

Washed and air-dried rhizomes of turmeric were used for preparing the extract. The rhizomes were blended and mixed with distilled water. The concentrate was filtered to obtain the juice extract which was refrigerated for use.

2.5.2. *Phytochemistry of Turmeric*

Turmeric powder is about 60-70% carbohydrates, 6-13% water, 6-8% protein, 5-10% fat, 3-7% dietary minerals, 3-7% essential oils, 2-7% dietary fiber, and 1-6% curcuminoids (Mahfouz *et al.,* 2009). Phytochemical components of turmeric include diarylheptanoids, a class including numerous curcuminoids, such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Khosropanah *et al.*, 2016). Curcumin constitutes up to 3.14% of assayed commercial samples of turmeric powder (the average was 1.51%); curry powder contains much less (an average of 0.29%). Some 34 essential oils are present in turmeric, among which turmerone, germacrone, atlantone, and zingiberene are major constituents (Li et al., 2015). Therefore, researchers have tried a wide range of tactics to increase curcumin's bioavailability (Joshi, A., Lehene, S., et al. 2023; Tabanelli, Brogi, and Calderone 2021).

2.5.3 Preparation of potash

Considerable quantities of Potash were purchased from Kersmond grocery stores, Ekpoma, Edo State. The Potash purchased was carefully poured on a clean dry plastic container. The potash was measured using an electric balance, packaged in small plastic envelopes, and stored until use. The substance preparation process was performed with maximum care in order to avoid any form of contamination.

2.5.4 Preparation of alcohol

Absolute ethanol (99.5%) was purchased from a pharmacy and used to induce gastric ulcer. Ethanol at the dose of 1 ml/rat and the concentration of 60% was used to induce ulcer as earlier described by Naito *et al.*, (2008).

2.5.5 Induction of ulcer

Ulcer was induced using ethanol and potash and the combination of both respectively to the grouping. 1 ml/rat of ethanol was administered.

2.5.6 Treatment

For one week the animals induced with ulcer were treated orally using aqueous turmeric extract through an oro-gastric tube to avoid spillage. Treatment started 3 hours after induction of ulcer.

2.6. *Surgical Procedures*

In the positive control groups without treatment, the rats were fasted 24 hours and then alcohol, potash and the combination were administered orally through the oro-gastric tubes to induce ulcer respectively. The rats were anesthetized using chloroform before they were sacrificed and the stomach harvested following standard laboratory procedures. Same was also done for the test group after the treatment period. The stomachs were opened along the lesser curvature and the stomachs were isolated and washed in normal saline.
Then, the stomachs were observed with the help of a hand magnifying lens, and its external and internal surface was studied and observed hemorrhage, dilation of blood vessels, ulceration, perforation, size and number of ulcers and ulcer index was evaluated according to the severity of ulcers (Vananenn *et al.*, 1991).

2.7 Sample Analysis

2.7.1. Determination of gastric ulcer index / ulcer score

Gross gastric lesion severity was measured as described by Wilhelmi and Menasse Gdynia (1972) using the 0 to 5 scoring system. Severity factor 1=1 or 2 minutes, sporadic, punctate lesion; 2= several small lesions; 3-one extensive lesions or multiple moderate sized lesions; 4 = several large lesions; 5= several large lesions with stomach perforation. The lesions score/ulcer index (UI) for each rat was calculated as the number of lesions in the rat multiplied by their respective severity factor. The UI for each group was taken as the mean lesion score of all the rats in that group.

2.7.2. Determination of percentage ulcer inhibition

The percentage of ulcer inhibition (%UI) was calculated by the equation of Hano et al. (1976).
%UI= {(UI of ulcer control - UI of treated)/ (UI of ulcer control)} x 100%

2.8 Data Analysis

The obtained data were then subjected to statistical analysis using SPSS (version 20). The test groups' values were compared with the values of the control group using ANOVA (LSD) at 95% level of confidence and $p<0.05$ was considered significant. Results were presented in suitable tables.

3. Results

3.1 Effect of Aqueous Turmeric (Curcuma longa) Extract on Gastric Ulceration Pits of Wistar Rats

Shown in Table 1 below are results from data analysis for mean ulcer pits of the groups induced with gastric ulcers and those treated using turmeric extract. The results showed a reduction in mean ulcer pits of test group B (1.25±0.01) following administration of turmeric extract compared to positive control group A1 (3.09±00.01). Also, ulcer pits in test group C (1.30±0.85) were decreased compared to positive control group A2 (2.07±0.22). However, there is a reduction in ulcer pits of test group D induced with alcohol and potash (2.03±0.11) compared to positive control group A1 (3.09±00.01) and A2 (2.07±0.22) respectively.

Table 1: Effect of aqueous turmeric extract on gastric ulceration pits of Wistar rats

Groups	Group A1	Group A2	Group B	Group C	Group D
Mean % Ulcer Pits	3.09 ± 0.01	2.07 ± 0.22	1.25 ± 0.01	1.30 ± 0.85	2.03 ± 0.11

n=6, P<0.05, Mean ± SD. Group A1 alcohol positive test group, group A2 potash positive test group, Group B, C, and D, aqueous turmeric extract treated groups.

3.2 Effect of Aqueous Turmeric (Curcuma longa) Extract on Percentage Ulcer Inhibition in Gastric Mucosa of Wistar Rats

Data in Table 2 shows greater inhibition of gastric ulcer in the groups treated with turmeric extract compared with control. Percentage ulcer inhibitions in test groups B (4.32±00.48) induced with alcohol was reduced compared to positive group A1 (5.04±00.12) while inhibition in test group C (1.09±00.01) was also reduced compared to positive control group A2 (2.08±01.00). Furthermore, reduced percentage inhibition was observed in test group D (2.01±00.66), induced with alcohol and potash compared to positive control group A1 (5.04±00.12) and A2 (2.08±01.00) respectively. The results were not statistically significant at $p< 0.05$.

Table 2: Effect of aqueous turmeric extract on percentage gastric ulcer inhibition in Wistar rats

Groups	Group A1	Group A2	Group B	Group C	Group D
Mean % Ulcer Inhibition	5.04 ± 0.12	2.08 ± 1.00	4.32 ± 0.48	1.09 ± 0.01	2.01 ± 0.66

n=6, P<0.05, Mean ± SD. Group A1 alcohol positive test group, group A2 potash positive test group, group B, C, and D, turmeric extract treated groups.

4. Discussion

This research finding shows that the extract of turmeric *(Curcuma longa)* exhibited significant protection against alcohol and potash-induced ulcer in Wistar rats by reducing mean ulcer scores in test groups (B=1.25±0.01, C=1.30±0.85, D=2.03±0.11) compared to control (A1=3.09±00.0, A2 =2.07±0.22). However, mean percentage inhibition rate in the treated groups (B=4.32±00.48, C=1.09±00.01, D=2.01±00.66) was lower compared to control (A1=5.04±00.12 and A2=2.08±01.00). This study agrees with earlier study by Anthwal et al., (2014) who found that ulcer was ameliorated with marked healing in the groups treated with aqueous turmeric extract while Prasad et al., (2014) describes both the anti-ulcer and ulcerogenic potential of turmeric. In another study, Salt extract of curcumin (sodium curcuminate), was found to inhibit intestinal spasm, increase bicarbonate while Curcuma powder has been reported to increase gastric wall mucus, in a study conducted by (Sankar *et al.*, 2016). Also, curcumin was found to increase mucin secretion in rabbits and may act as a gastroprotective agent against irritants (Ravindran, 2007).
The present study however supports the traditional use of this plant against gastric problems. Preliminary phytochemical screening of extract of turmeric showed the presence of triterpenes. In a study conducted by Faber *et al*. it was found that anti-ulcer activity of turmeric is due to the presence of terpenes (Sharma *et al.,* 2004). Also, turmeric has been reported to be highly effective in suppressing *Helicobacter pylori* in the stomach. Research has shown that turmeric inhibits the shikimate path required for the synthesis of the bacteria aromatic ring, and therefore its growth. The histological analysis in the same study showed that turmeric also restores damaged cell walls of the stomach caused by *Helicobacter pylori* (Majeed *et al.,* 2000).

5. Conclusion

This study concluded that turmeric extract (Curcuma longa) offers significant protection against alcohol and potash-induced gastric ulcers in Wistar rats. That curcumin acts as gastroprotective agent against irritants. This study has revealed that turmeric extract has significant anti-ulcer activity. This healing ability is however attributed to its rich phytochemicals. The anti-ulcer activity is attributed to the presence of triterpenes and terpenoids.

6. Recommendation

Even though the present study shows significant ulcero-protective action of the aqueous extract of *Curcuma longa,* its precise mechanisms of action are not clear. Further research is needed to determine the precise processes / mechanisms underlying its anti-ulcer activity.

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References

Ak, T. and Gülçin, I. (2008): Antioxidant and radical scavenging properties of curcumin. *Chemico- Biological Interactions,* 174 (1), 27-37.

Anthwal, A., Thakur, B.K. and Rawat, M.S. (2014): Synthesis, characterization and in vitro anticancer activity of C- 5 curcumin analogues with potential to inhibit TNF- a-induced NF-κ B activation. *Biomed Res. Int.* (10):52-161.

Bar-Sela, G., Epelbaum, R. and Schaffer, M. (2010): Curcumin as an Anti- Cancer Agent:
Review of the Gap Between Basic and Clinical Applications. *Curr Med Chem* 17 (3): 190-197.

Basnet, P. and Skalko-Basnet, N. (2011): Curcumin: An Anti-Inflammatory Molecule from a Curry Spice on the Path to Cancer Treatment. *Molecules* 16, 4567-4598.

Chong, L., Zhang, W. and Nie, Y. (2014): Protective effect of curcumin on acute airway inflammation of allergic asthma in mice through Notch1-GATA3 signaling pathway. *Inflammation* 37:1476-1485.

Domper Arnal, María-José, Gonzalo Hijos-Mallada, and Angel Lanas. 2022. "Gastrointestinal and Cardiovascular Adverse Events Associated with NSAIDs." Expert Opinion on Drug Safety 21 (3): 373–84. https://doi.org/10.1080/14740338.2021.1965988.

Douglass, B.J. and Clouatre, D.L. (2015): Beyond Yellow Curry: Assessing Commercial Curcumin Absorption Technologies. J *Am Coll Nutr* 34 (4):347-358.

Fiala, M. (2015): Curcumin and Omega-3 Fatty Acids Enhance NK Cell- Induced Apoptosis of Pancreatic Cancer Cells but Curcumin Inhibits Interferon-y Production: Benefits of Omega-3 with Curcumin against Cancer. *Molecules* 20:3020-3026.

FDA. Curcumin—FDA GRAS Report. Available online: **https://www.fda.gov/media/132575/download** (accessed on 22 August 2024).

Gulcubuk, A., Haktanir, D. and Cakiris, A. (2013): Effects of curcumin on proinflammatory cytokines and tissue injury in the early and late phases of experimental acute pancreatitis. *Pancreatology* 13 (4):347-354.

Huang, H., Chen, X., Li, D., He, Y., Li, Y., Du, Z., Zhang, K, Di, P., Goodin, S., Zheng, X. (2015): Combination of a-Tomatine and Curcumin Inhibits Growth and Induces Apoptosis in Human Prostate Cancer Cells. *PLOS One* 10 (12):1-3.

Hussein, S. A., El Senosi, Y.F., Hassanien, M.R and Hammad, M. F. (2016): Ameliorative Effect of Curcumin on Hepatic Oxidative Stress, Antioxidant Status, Cardiac Markers Enzymes and Inflammation in High Cholesterol Diet- Induced Hypercholesterolemia in Rats. *Int. J. Pharm.* 6 (3):1496-1505.

Jayaprakasha, G.K., Jaganmohan Rao, L. and Sakariah, K.K. (2006): Antioxidant activities of curcumin, demethoxycurcumin and bisdemethoxycurcumin. *Food Chem* 98:720-724.

Joshi, A., Lehene, S., Lasnapure, B. *et al.* Investigation of antioxidant, anti-ulcer, and analgesic potential of a metal-curcumin complex. *Naunyn-Schmiedeberg's Arch Pharmacol* **396**, 1043–1052 (2023). https://doi.org/10.1007/s00210-022-02381-6

Kandiannan, K., Thankamani, C.K., Srinivasan, V. and Rajeev, P. (2008): Turmeric (Extension Pamphlet), Indian Institute of Spices Research. *Food Chem* 8:30-63.

Kasinski, A.L., Du, Y., Thomas, S.L., Zhao, J. and Sun, S.Y. (2008): Inhibition of IκB kinase-nuclear factor-κB signaling pathway by 3,5- bis(2-chlorobenzylidene) piperidin-4-one (EF24), a novel monoketone analog of curcumin. *Mol. Pharmacol*. 74:654-661.

Khosropanah, M. H., Dinarvand, A. and Nezhadhosseini, A. (2016): Analysis of the Antiproliferative Effects of Curcumin and Nanocurcumin in MDA-MB231 as a Breast Cancer Cell Line. *Iran* J *Pharm Res*. 15 (1):231-239.

Li, J., Xiang, S. T., Zhang, QH., Wu, JJ., Tang, Q., Zhou, JF., Yang, LJ., Chen, ZQ. and Hann, S. S. (2015): Combination of curcumin and bicalutamide enhanced the growth inhibition of androgen- independent prostate cancer cells through SAPK/JNK and MEK/ERK1/2-mediated targeting NF-κB/p65 and MUC1-C. J. Exp. *Clin. Cancer Res*. 34 (1):4-6.

Mahfouz, M.M., Zhou, S.Q. and Kummerow, F.A. (2009): Curcumin prevents the oxidation and lipid modification of LDL and its inhibition of prostacyclin generation by endothelial cells in culture. *Prostaglandins & other Lipid Mediat*. 90 (1-2):13-20.

Majeed, M., Badmaev, V., Shivakumar, U. and Rajendran, R. (2000): Research Report from Sabinsa Corporation in Sabinsa Corporation in Curcuminoids: *Antioxidant* online *phytonutrients,* www.curcuminoids.com/antioxidant.htm, 2000.

Parvathy, K. S., Negi, P., Srinivas, P. (2009): Antioxidant, antimutagenic and antibacterial activities of curcumin-diglucoside. Food *Chem*. 115 (1):265-271.

Prasad, S., Tyagi, A. K. and Aggrawal, B. B. (2014): Recent Developments in Delivery, Bioavailability, Absorption and Metabolism of Curcumin: The Golden Pigment from Golden Spice. *Cancer Res Treat.* 46 (1):2-18.

Ravindran, P. N. (2007): Turmeric - The Golden Spice of Life in Turmeric: the genus Curcuma edited by P.N. Ravindran, K. Nirmal Babu, and K. Sivaraman. *Medicinal and aromatic plants--industrial profiles*. 45:4-43

Sankar, P., Telang, A. G., Kalaivanan, R., Karunakaran, V., Suresh, S. and Kesavan, M. (2016): Oral nanoparticulate curcumin combating arsenic-induced oxidative damage in the kidney and brain of rats. *Toxicol Ind Health.* 32 (3):410-421.

Sharma, R. A., Euden, S. A., Platton, S. L. and Cooke, D. N. (2004): Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. *Clin. Cancer Res*. 10
(20):6847-54.

Shen, Cai-Hong, Cui-Ting Liu, Xiao-Juan Song, Wei-Ya Zeng, Xiao-Ying Lu, Zuo-Liang Zheng, Jie-Pan, Ruo-Ting Zhan, and Ping-Yan. 2018. “Evaluation of Analgesic and Anti-Inammatory Activities of Rubia Cordifolia L. by Spectrum-Effect Relationships.” Journal of Chromatography B 1090: 73–80. https://doi.org/10.1016/j.jchromb.2018.05.021.

Tabanelli, Rita, Simone Brogi, and Vincenzo Calderone. 2021. “Improving Curcumin Bioavailability: Current Strategies and Future Perspectives.” Pharmaceutics 13 (10). https://doi.org/10.3390/pharmaceutics13101715.

Tian, Chunlian, Yu Chang, Zehui Zhang, Hong Wang, Shibo Xiao, Cancan Cui, and Mingchun Liu. 2019. “Extraction Technology, Component Analysis, Antioxidant, Antibacterial, Analgesic and Anti-Inammatory Page 17/19 Activities of Flavonoids Fraction from Tribulus Terrestris L. Leaves.” Heliyon 5 (8): e02234. https://doi.org/10.1016/j.heliyon.2019.e02234.

Zhao, Jun, Aosimanjiang Maitituersun, Chenyang Li, Qian Li, Fang Xu, and Tao Liu. 2018. “Evaluation on Analgesic and Anti-Inammatory Activities of Total Flavonoids from Juniperus Sabina.” Edited by Roberto K. N. Cuman. Evidence-Based Complementary and Alternative Medicine 2018 (July): 7965306. https://doi.org/10.1155/2018/7965306.