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Full length Research Article

Low Dose Potassium Bromate Enhances Ischemic Reperfusion-induced Gastric Ulcer Healing in Thyroidectomised Rats

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Summary: Gastric ulcer healing is impaired in both hypothyroid and hyperthyroid conditions. Thyroid hormones regulate growth, energy metabolism and mitochondrial oxidative metabolism. Xenobiotics have been documented to negatively impact the thyroid gland at high doses but the redox and cellular interactions at low doses during wound healing process remains unclear. Potassium bromate has been documented to be toxic at high doses but there is dearth of information on its activities at a low dose in varied thyroid states which was evaluated in this study. 60 male Wistar rats (g, n=10) were randomised into 2 conditions: Normal, ulcerated untreated, ulcerated treated with 12.5mg/kg p.o KBrO3 and thyroidectomised groups: thyroidectomised ulcerated, thyroidectomised ulcer treated with KBrO3 and thyroidectomised treated with thyroxine (100µg/kg) Total thyroidectomy was used to model hypothyroidism, and ischaemia-reperfusion-induced gastric ulcers were monitored for healing. Daily body weights, Levels of thyroxine, Gastric mucin content, redox and sodium pump activity were examined alongside other markers of hepatic and haematological toxicity by days 3 and 7 post ulceration. Data were analysed using descriptive statistics and ANOVA α 0.05. The bromate-exposed hypothyroid rats showed increased gastric ulcer healing potential with reduced gastric epithelial oedema and inflammation; hepatic steatosis, and periportal inflammation. Haematological variables and markers of hepatic functions were normal. There were reduced levels of gastric and hepatic malondialdehyde levels. Thyroxine and potassium bromate treatment resolved the redox and cellular toxicity possibly via increasing catalase and sulfhydryl levels and increased Na+ K+ pump activity. We conclude that potassium bromate enhanced gastric ulcer healing in hypothyroid state, similar to thyroxine treatment.

Keywords*: Thyroidectomy, potassium bromate, inflammation, Gastric ulcer, renal function, hepatic function.*

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INTRODUCTION

Gastric ulcer healing is a complex process involving various phases such as haemostasis, inflammatory, angiogenesis, proliferative re-epithelization (Fagundes *et al*., 2020, Si *et al*., 2005; Miyake *et al*., 1980) just to mention a few. It is a process in which breached epithelium (gastric ulcer) mostly within the gut, heal formed wound. This involves several other systems like the blood, neuroendocrine (Hampton and Hale, 2011; Waldum *et al*., 2019) and endocrine cells/systems within the body (Sorbye and Svanes 1994, Salami *et al*., 2021). Various hormones have been documented to be implicated / enhanced during gastric ulcer healing few of these include testosterone (Machowska *et al*., 2004), growth (Beckert *et al*., 2004, Akpamu *et al*., 2016), gastrin (Batisa *et al*., 2015) gherline and leptin (Khalefa *et al*., 2010) as well as thyroid (Namulema *et al*., 2018) hormones.

The hypothalamic-pituitary-thyroid (HPT) axis primarily maintains circulating thyroid hormone levels via a negative feedback loop involving thyroid stimulating hormone (TSH; thyrotropin) release from the anterior pituitary gland, which is influenced by the hypothalamic thyrotropin-releasing hormone (TRH) and the thyroid hormones (Brent, 2012). The regulatory activity of the thyroid hormone requires activation of the prohormone thyroxine (T_4) to triiodothyronine (T_3). T_3 then interacts with cellular and tissue-specific thyroid hormone receptors, corepressors and coactivators both in the thyroid hormone signalling pathway and its cross-talk with other signalling pathways (Cheng *et al*., 2010). Thyroid hormones regulate energy metabolism while increasing basal metabolic rate (BMR) and oxidative metabolism (Shahid *et al*., 2022).

Consequently, reactive oxygen species (ROS) are generated as by-products of mitochondrial oxidative metabolism, which is exacerbated in the hyperthyroid state (Das and Chainy, 2001; Venditti and Di Meo, 2006). However, hypothyroidism may not influence existing oxidative stress, but increased levels of thiobarbituric acid reactive substances (TBARS) have been detected in the plasma of hypothyroid subjects, and T3 treatment mitigates the production of redox active species in hypothyroid rats (Das and Chainy, 2001; Gredilla *et al*., 2009; Kebapcilar *et al*., 2007), suggesting that both hypothyroidism and hyperthyroidism can predispose to redox imbalance. Conversely, the thyroid hormone is crucial for would healing in in vitro, in vivo and ex vivo systems as T3 has been linked with improved re-epithelialisation, angiogenesis, and vasodilation via the nitric oxide pathway (Adeniyi *et al*., 2018; Post *et al*., 2021; Salami *et al*., 2016; Zhang *et al*., 2019).

The solubility and stability of bromate in water, alongside the limitations in analytical methods and treatment technologies currently make bromate eradication from drinking water difficult, but a strict benchmark of 10 µl/L in drinking water is enforced across several regions (Bromate CASRN 15541-45-4 | IRIS | US EPA; Deangelo *et al*., 1998). Despite ozone's potential for disinfecting and reducing micropollutants in water, it may oxidize bromide in source water to form toxic bromate residue (Bonacquisti, 2006). Bromate may also be present in water due to other oxidation processes like chlorination, sulphate and ferrate-based oxidation, as well as from industrial effluents and road runoff into water bodies. (Zhang and Jiang, 2022). Bromide in water is oxidized to bromate, and bromate when ingested is converted to bromide invivo (Kurokawa *et al*., 1990; Abuelgasim *et al*., 2008). In individuals who have been accidentally exposed to higher bromate doses, there have been reports of rapid gastrointestinal absorption and irritation, renal failure, and reduced neurological function due to central nervous system depression (Gradus (Ben-Ezer) *et al*., 1984; Matsumoto *et al*., 1980). However, some bromide containing compounds and drugs like Methscopolamine bromide, Penthienate bromide (Ivey, 1975), Salt-bromine-iodine mineral water (Albertini *et al*., 2007), clidinium bromide (Eskander *et al*., 2013), Glycopyrronium bromide (Baume *et al*., 1972) and methantheline bromide (Liebowitz *et al*.,1952) have been used in the treatment of peptic ulcer.

Based on previous information on the displacement effect of halogens (-chloride and iodide) by bromide in vivo (Pavelka, 2004), it has been shown to concentrate majorly in the stomach and thyroid gland which contain halogens also called Schiff bases. Several researches have been documented as regards improved gastro-protective activities of chelated Schiff bases (halogens) especially chlorine (Jaisankar *et al*., 2018). Schiff based derived bromine exerts gastro-protection during ethanol induced gastric ulcer (Saremi *et al*., 2019). However, little information exists on the gastroprotective activities of bromine (a chelated Schiff base derived from potassium bromate) in hypothyroid states despite the ability of Schiff based bromine concentrates in the stomach and thyroid. This research was investigated to evaluate the gastro-protective activities of potassium bromate in hypothyroid states.

MATERIALS AND METHODS

Drugs and reagents: Levothyroxine Sodium was purchased from Mercury Pharma (Generics) Ltd., Croydon, UK and Procaine Penicillin was purchased from Guorui Pharmaceutical Co. Ltd., China. ELISA kits for Thyroid assay (T3, T4, TSH) were purchased from Cal Biotech Incorporation, Spring Valley, California, USA. All reagents were of analytical grade.

Potassium bromate: Animals were administered potassium bromate at a dose of 12.5mg/kg b.w orally. This dose is far lower than the LD50 of potassium bromate which is 215 mg/kg in Wistar rats and 464 mg/kg in ICR mice (Dongmei *et al*., 2015).

Experimental design: 60 male Wistar rats weighing 120 – 140 g were housed at the Central Animal House, Department of Physiology, College of Medicine, University of Ibadan, Nigeria. Approval was given before the commencement of experiment from the University of Ibadan, Animal Care and Use Research Ethics Committee (ACUREC) and assigned a number UI-ACUREC/19/0074. A two-week acclimatization period was ensured at standard experimental conditions, namely: 23 - 25oC room temperature, 55% relative humidity and 12 hr light / 12 hr dark cycle. Animals had free access to water and feed (Ladokun commercial rat diet, Nigeria), and were randomly assigned to groups (n=10), including: 1-Control [Normal], 2-Ulcer [UU], 3-Ulcer + 12.5 mg/kg KBrO3 (Kurokawa *et al*., 1990) [UK], 4-Ulcer + Thyroidectomy [UT], 5-Thyroidectomy + Ulcer + 100µg/kg thyroxine (Salami *et al*., 2016) [TUT], 6-Thyroidectomy + Ulcer + 12.5 mg/kg KBrO3 [TUK]

Thyroidectomy was induced at the start of the experimental period, then animals were observed for 35 days before gastric ulcer induction. Weights were recorded bi-weekly and animals were sacrificed on post-ulcer induction days 3 and 7 for further analysis.

Thyroidectomy and gastric ulcer induction: Animals were placed under anaesthesia (5 mg/kg b.w Xylazine and 60 mg/kg b.w Ketamine) for all surgical interventions. Thyroidectomy entailed removal of the thyroid gland via a midline incision in the neck, while leaving the parathyroid gland and recurrent laryngeal nerves intact (Salami *et al*., 2016). Gastric ulcer was induced by altering ischemia and reperfusion to the stomach (Wada *et al*., 1996, Salami *et al*., 2017). The left gastric artery was clamped for 30 mins and freed to allow reperfusion of the gastric tissue.

Thyroid function, haematology profile, renal and hepatic function test: Whole blood was collected from the rat retro orbital sinus into Ethylene Diamine Tetra acetic Acid (EDTA) bottles for thyroid function test, haematological profiling, plasma protein, plasma electrolyte and plasma lipid content, as well as renal and hepatic function test. Thyroid hormones were assayed via Enzyme-Linked Immuno-Sorbent Assay (ELISA) according to the protocols highlighted by the kit manufacturer (Cal biotech, El Cajon, CA). The reaction was based on a solid phase competitive ELISA with an analytical sensitivity of 1 µg/dl for thyroxine (T4), 0.25 ng/ml for triiodothyronine (T3) and 0.5 µlU/ml for thyroid stimulating hormone (TSH). Briefly,

samples were conjugated alongside the relevant enzyme to polyclonal antibody coated well. Unbound enzyme and enzyme conjugates were washed off before substrate addition. A standard curve was prepared and used to interpolate colour intensity to enzyme concentration.

Haematological profiling was based on established protocols. They included the evaluation of packed cell volume (PCV) (Sorokin, 1973), red blood cell count (RBC) (Rowan, 1983), haemoglobin concentration (Hb) (van Lerberghe *et al*., 1983), total white blood cell (TWBC) (Rowan, 1983), differential white blood cell count (Burstein, 2007) and platelet count (Brecher and Cronkite, 1950). Plasma protein, plasma electrolyte, plasma lipid content, as well as renal and hepatic function test were analysed as earlier described (Elinder *et al*., 1985; Gregor *et al*., 1977).

Macroscopic and microscopic examination of gastric epithelium: Excised rat stomach was cut open across the greater curvature, rinsed in normal saline to rid food debris and spread out to macroscopically examine for ulceration. Degree of ulceration was scored using a 2X magnifying lens as follows: normal stomach – 0; red coloration – 0.5; spot ulcer – 1; haemorrhagic streaks – 1.5; ulcers > 3mm < 5mm – 2; ulcers > 5mm – 3 (Kunchandy *et al*., 1985).
5µm stomach and liver sections were fixed in 10 % formalin and embedded in paraffin. Stained sections (Haematoxylin and Eosin (H&E) stain) were microscopically examined for inflammation, granulation, regeneration and vascular integrity. Pathophysiological changes were shown on a microphotograph.

Stomach and liver tissue preparation: Homogenised stomach and liver tissue was centrifuged (10,000 RPM x 4oC x 10 mins) and decanted supernatant was stored at -20oC for biochemical analysis. Protein concentration of gastric and hepatic tissue was estimated via a slight modification of the method described by (Gornall *et al*., 1949). CU2+ precipitation to Cuprous Oxide was prevented by the addition of Potassium the Biuret reagent.

Evaluation of oxidative stress (MDA, Protein Carbonyl) and antioxidant activity (SOD), Sulfhydryl, mucin, Nitric oxide and Sodium Potassium ATPase activity: The production of malondialdehyde (MDA) during lipid peroxidation of cellular membranes was used as a marker of oxidative stress, as thiobarbituric acid reactive substances (TBARs) react with MDA to form a pink solution whose light absorbance can be read at 532 nm (Varshney and Kale, 1990).

Protein carbonyl assay was based on the reaction of carbonyl groups with 2,4-dinitrophenylhydrazine to form the 2,4-dinitrophenylhydrazone (Levine *et al*., 1990).
Superoxide dismutase (SOD) and catalase activity were monitored as markers of antioxidant activity via the methods described by (Misra and Fridovich, 1972) and (Claiborne, 1985) respectively.

The estimation of nonprotein sulfhydryl content of gastric and hepatic tissues relied on (Ellman, 1959) determination that a mole 2-nitro-5-mercaptobenzoic acid is formed for each mole of sulfhydrl that reduces 5,5'-dithiobis-(2-nitrobenzoic acid) (Sedlak and Lindsay, 1968). The diazotizing agent – sulfanilamide, and the coupling agent – N-(1-naphthyl) ethylenediamine constitute the Griess reagent that reacts with nitrite to form a highly coloured azo dye readable at an absorbance of 548 nm (Ignarro *et al*., 1987). The estimated total nitrite is used as an indirect quantification of nitric oxide (NO) levels (Salami *et al*., 2016). Mucin contains hexose that reacts with orcinol (5-methyl resorcinol) in the presence of sulfuric acid, yielding a spectrophotometrically measurable coloured product (Winzler, 2006). Conversely, the incubation of biological membranes with adenosine triphosphate releases phosphate that is used as a measure of sodium potassium pump activity (Bewaji *et al*., 1985).

Statistical analysis: Data was analysed using two-way ANOVA with Tukey's post hoc test on GraphPad Prism 7 and presented as Mean ± Standard Error of Mean (S.E.M). p-value < 0.05 was considered statistically significant.

RESULTS

Body weight change and thyroid hormone levels: Thyroid hormone levels (TSH, T4, T3) were significantly reduced in thyroidectomised rats throughout the experimental period (Figure 1). There was also a significant reduction in percentage body weight in thyroidectomised (hypothyroid) rats exposed to potassium bromate compared with potassium bromate treated euthyroid rats (Figure 2).

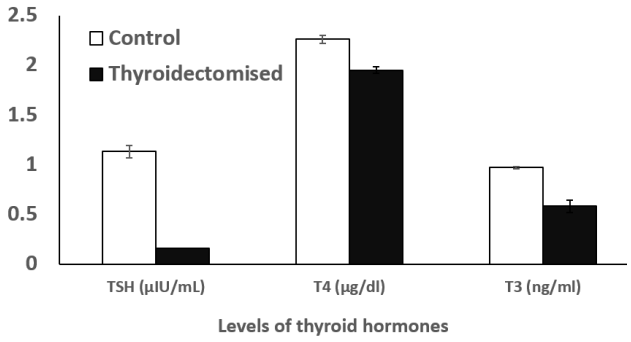

Figure 1
Thyroid hormones levels in control and thyroidectomised rats

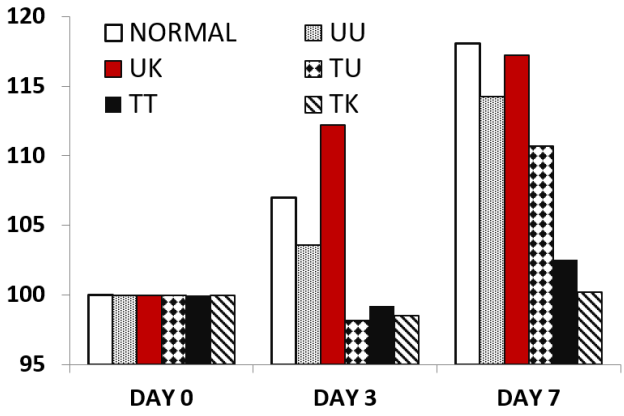

Figure 2:
Effect of potassium bromate on percentage body weight in euthyroid and hypothyroid states. NORMAL - Control; UU-ulcerated untreated; UK - Ulcerated treated with 12.5mg/kg/day of Potassium Bromate; TU - Thyroidectomised ulcerated untreated; TUT - Thyroidectomised ulcerated treated with (100µg/kg/day) of Levothyroxine; TUK - Thyroidectomised ulcerated treated with 12.5mg/kg/day of Potassium Bromate.

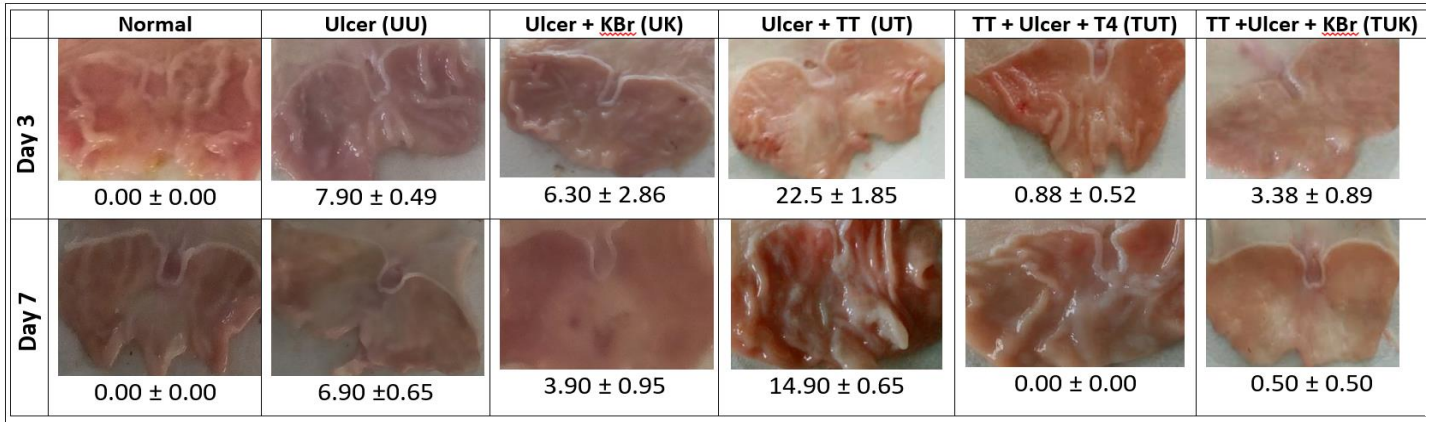

Plate 1:
Gastric tissue and mean ulcer score across groups

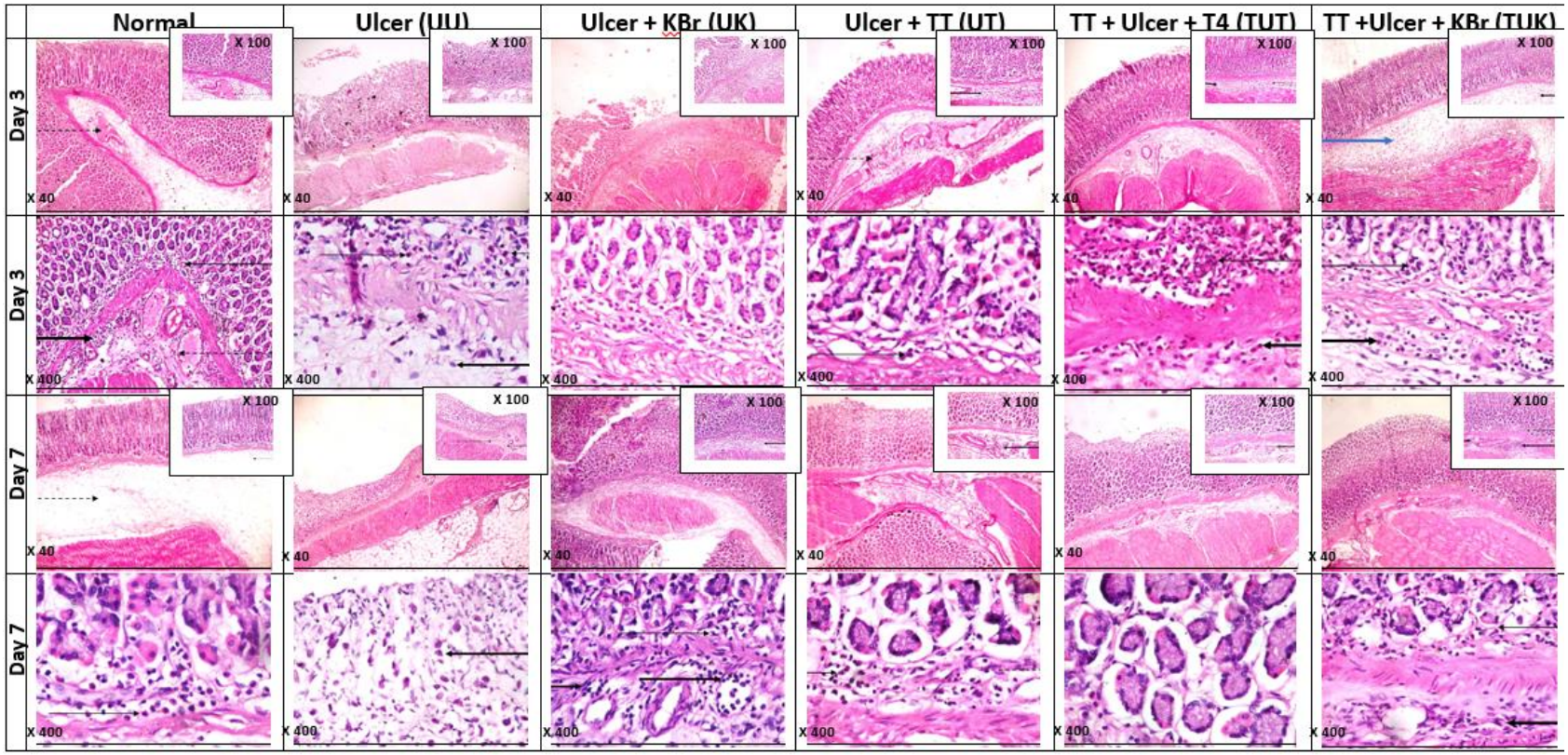

Plate 2:
Gastric tissue photomicrograph at Days 3 and 7, observed using haematoxylin and eosin stains at X 40, X 100 and X 400 magnification.

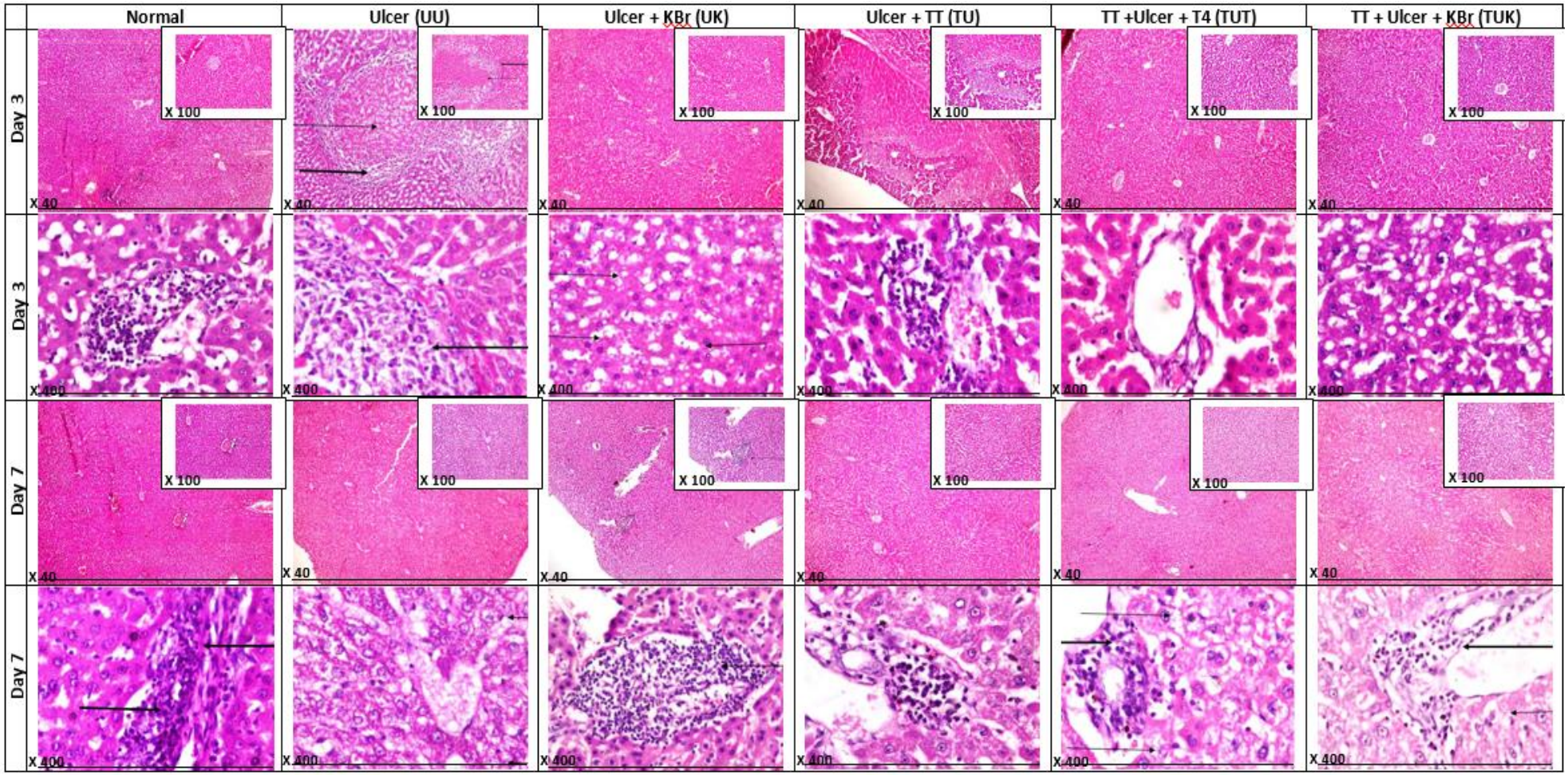

Plate 3:
Hepatic tissue photomicrograph at Days 3 and 7, observed using haematoxylin and eosin stains at X 40, X 100 and X 400 magnification

Gastric and hepatic epithelial integrity: Euthyroid and Hypothyroid state and/or potassium bromate exposure significantly decreased the severity of gastric ulcers formed during ischaemia and reperfusion of the gastric tissue compared with ulcerated untreated in euthyroid and hypothyroid states. Consequently, thyroxine treatment ameliorated the gastric ulcers in hypothyroid state (Plate 1).

Plate 2 shows gastric tissue photomicrographs during bromate exposure across thyroid states. By day 3, a focal area of angiogenesis with vascular congestion (dashed arrow) was observed in the control group. The Ulcer + 12.5 mg/kg KBrO3 and Ulcer + Thyroidectomy + 12.5 mg/kg KBrO3 groups showed mild ulceration of the mucosa with chronic inflammation of the submucosa and muscularis mucosa. The inflammatory cells were still present in the thyroxine treated group, but there was substantial adipocyte and fibroblast infiltration into the submucosa. By day 7, there were mild inflammatory cells into the mucosa and moderate infiltration into the submucosa persisted in the Ulcer + 12.5 mg/kg KBrO3 and Ulcer + Thyroidectomy + 12.5 mg/kg KBrO3 groups there were still mild inflammatory cells infiltration into the mucosa and submucosa in the thyroxine treated group.

Plate 3 shows hepatic tissue photomicrographs during bromate exposure across thyroid states. By day 3, the presence of vascular congestion, thrombosis, and cirrhosis with large regenerative nodules surrounded by thick fibrous connective tissue embedded with chronic inflammatory cells was observed in the ulcerated group. The Ulcer + 12.5 mg/kg KBrO3 and Ulcer + Thyroidectomy + 12.5 mg/kg KBrO3 groups showed focal area of mild steatosis, thrombosis, vascular congestion, periportal inflammation, the replacement of hepatocytes with fibrous connective tissue, and a focal area of well encapsulated cyst with heavy presence of inflammatory cells. However, normal hepatocytes were observed with no significant lesions in the thyroxine treated group. By day 7, the pathologies persisted with focal area of necrosis and mild steatosis in the ulcerated, in the Ulcer + 12.5 mg/kg KBrO3 and Ulcer + Thyroidectomy + 12.5 mg/kg KBrO3 groups there were disseminated mild steatosis, focal area of sinusoidal dilation and congestion, but there was no difference in photomicrographs of the control group and the Ulcer + Thyroidectomy + 100µg/kg thyroxine group.

Biochemical modifications: Figures 3 & 4 show alterations in oxidative stress, antioxidant activity markers, sodium pump activity, and mucin content in gastric tissue during bromate exposure across thyroid states. In all thyroidectomised groups (Ulcer + Thyroidectomy, Ulcer + Thyroidectomy + 100µg/kg thyroxine, Ulcer + Thyroidectomy + 12.5 mg/kg KBrO3), there was significant reduction in the detection of malondialdehyde (MDA), carbonyl and nitric oxide (NO). Conversely, there were increased nitric oxide (NO) levels, sodium pump (Na+ K+-ATPase) activity, and mucin content in potassium bromate and thyroxine treatment.

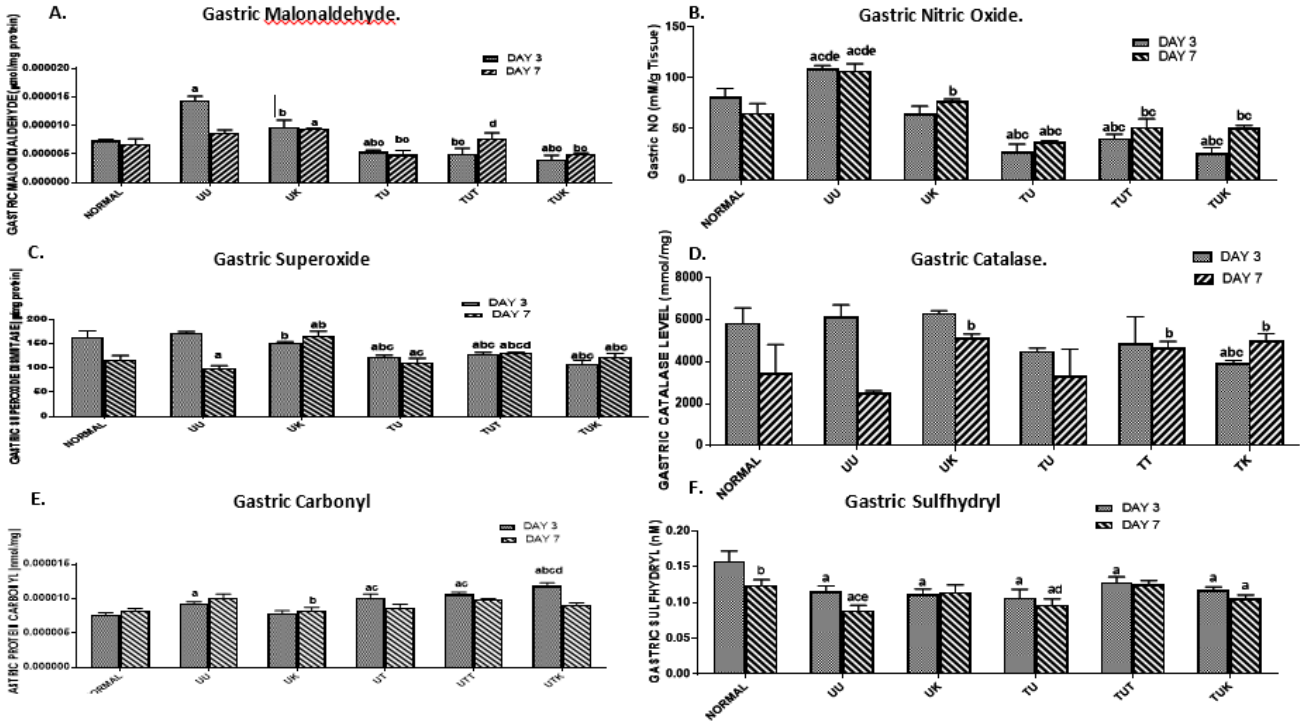

Figure 3:
Effect of potassium bromate on redox changes in the stomach in euthyroid and hypothyroid states. (A) Malonaldehyde levels across groups (B) Nitric oxide levels across groups (C) Superoxide dismutase activity across groups (D) Catalase activity across groups (E) Carbonyl levels across groups (F) Sulfhydrl levels across groups. [a] significant compared with animals in control (NORMAL), [b] significant compared with animals in ulcerated untreated group (UU), [c] significant compared with animals in ulcerated treated with potassium bromate group (UK), [d] significant compared with animals in thyroidectomized ulcerated untreated group (TU), [e] significant compared with animals in thyroidectomized ulcerated treated with levothyroxine group (TUT), [f] significant compared with animals in thyroidectomized ulcerated treated with potassium bromate group (TUK). Values are expressed as Mean ± SEM and are considered statistically significant when p value < 0.05

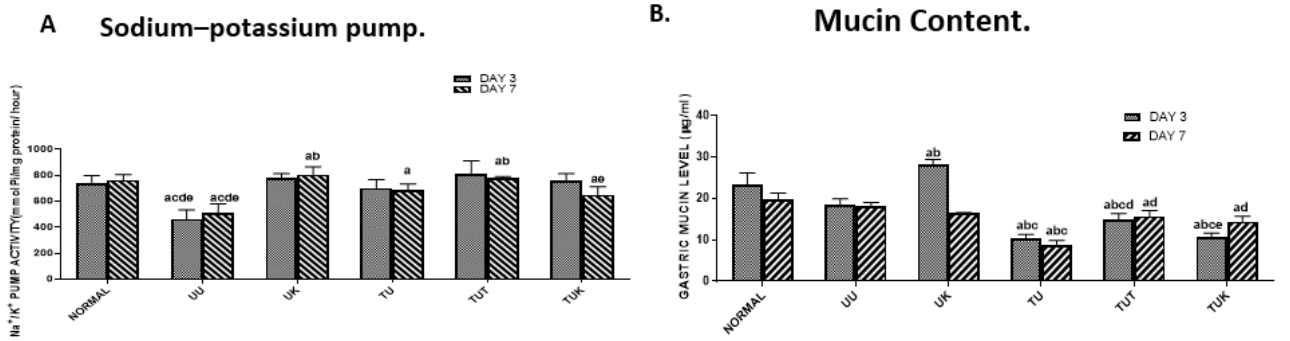

Figure 4:
Effect of potassium bromate on (A) sodium–potassium pump and (B) mucin content in the stomach during euthyroid and hypothyroid states. [a] significant compared with animals in control (NORMAL), [b] significant compared with animals in ulcerated untreated group (UU), [c] significant compared with animals in ulcerated treated with potassium bromate group (UK), [d] significant compared with animals in thyroidectomized ulcerated untreated group (TU), [e] significant compared with animals in thyroidectomized ulcerated treated with levothyroxine group (TUT), [f] significant compared with animals in thyroidectomized ulcerated treated with potassium bromate group (TUK). Values are expressed as Mean ± SEM and are considered statistically significant when p value < 0.05

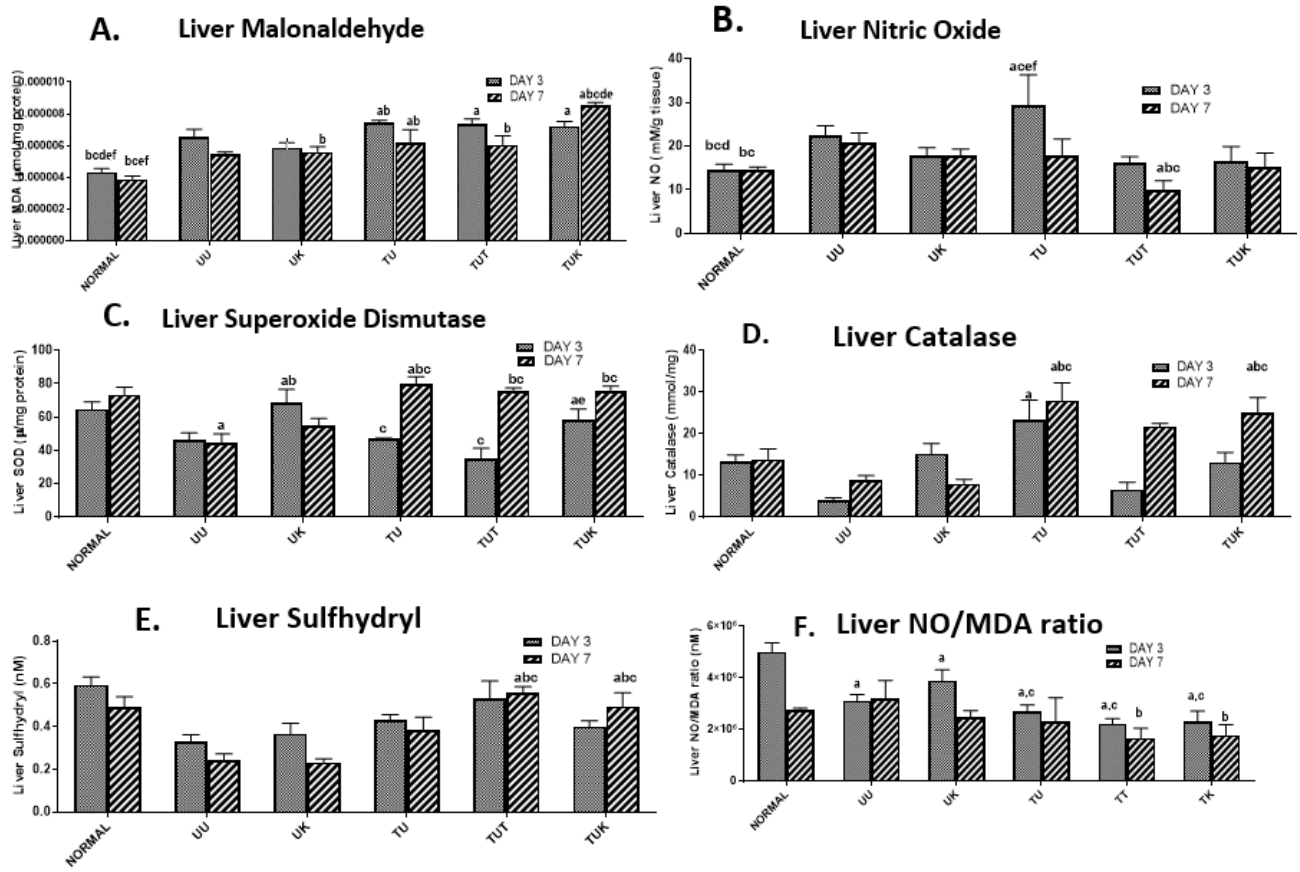

Figure 5:
Effect of potassium bromate on redox changes in the liver in euthyroid and hypothyroid states. (A) Malonaldehyde levels across groups (B) Nitric oxide levels across groups (C) Superoxide dismutase activity across groups (D) Catalase activity across groups (E) Sulfhydrl levels across groups (F) Nitric oxide / Malonaldehyde ratio across groups. a significant compared with animals in control (NORMAL), b significant compared with animals in ulcerated untreated group (UU), c significant compared with animals in ulcerated treated with potassium bromate group (UK), d significant compared with animals in thyroidectomized ulcerated untreated group (TU), e significant compared with animals in thyroidectomized ulcerated treated with levothyroxine group (TUT), f significant compared with animals in thyroidectomized ulcerated treated with potassium bromate group (TUK). Values are expressed as Mean ± SEM and are considered statistically significant when p value < 0.05

Figure 5 shows alterations in biochemical parameters in hepatic tissue during bromate exposure across thyroid states. Bromate exposure in hypothyroid state significantly increased hepatic MDA levels compared with bromate exposure in euthyroid state, and thyroxine treatment restored MDA levels within the control range (by day 7). SOD and catalase levels were also significantly increased in thyroidectomised groups, while thyroxine treatment increased sulfhydryl levels.

Table 1:
Effect of potassium bromate on red cell parameters and platelets (PLT) in euthyroid and hypothyroid states

	PCV (%)		Hb (g/dL)		RBC (x10^{6}L)		RTIC (%)		MCH (pg)		MCV (fL)		MCHC (%)		PLT (mm^3)	
GRP	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**
NL	41.33 ± 1.33	42.0 ± 0.58	13.73 ± 0.29	14.3 ± 0.17	7.70 ± 0.24	7.24 ± 0.06	2.93 ± 0.03	2.93 ± 0.03	19.74 ± 0.15	19.74 ±0.15	60.38 ± 0.78	58.44± 0.07	32.91± 0.55	33.32± 0.37	142667± 1763.83	174000± 6429.10
UU	45.33± 0.33[a]	39± 1.00	14.7± 0.15	12.63± 0.19[a]	7.4 1± 0.04	7.16 ± 0.21	3.3 ± 0.06[a]	2.7 ± 0.00	19.55 ± 0.00	19.86 ±0.05	61.16 ±0.73	60.86 ± 0.13	32.37 ± 0.07	33.08 ± 0.33	110667 ± 3929.94[a]	244000 ± 8504.9[a]
UK	45.33± 0.33[a]	43.33± 0.33[b]	14.57± 0.13	14.53± 0.09[b]	7.34± 0.05	7.35± 0.02	3.17± 0.09	3.1± 0.06[b]	20.12± 0.09	19.78± 0.07	61.76 ± 0.31	60.29± 1.34	32.50± 0.16	33.5± 0.36	119333.33± 5696	244666.67± 6359.59[a]
TU	44 ± 0.58	39.33± 0.33[c]	14.37± 0.58	13.03± 0.28[c]	7.32± 0.03	6.66± 0.28	3.03± 0.15	2.13± 0.07[abc]	20.39± 0.26[b]	19.61± 0.38	61.05 ± 0.23	60.17± 0.96	32.92± 0.20	32.59± 0.13	162666.67± 7423.69[bc]	163333.33± 15025.90[bc]
TUT	42.67± 0.88	41.33± 0.33	13.93± 0.35	13.50± 0.25	7.16± 0.25	7.24± 0.25	3.20± 0.12	2.03 ± 0.03[abc]	19.47± 0.29[d]	20.12± 0.14	59.63 ± 0.98	61.09± 0.28	32.65± 0.16	32.47± 0.17	126000± 5131.6[d]	117000± 3214.55[abcd]
TUK	40.33± 0.33[bcd]	42.33± 1.20[b]	13.36± 0.12[b]	13.57± 0.47	6.55± 0.04[abcd]	6.89 ±0.22	3.20± 0.06	2.37 ± 0.03[abce]	20.39± 0.22[be]	19.69± 0.07	61.55 ± 0.38	58.94± 0.48	33.42± 0.29	33.23± 0.25	143000± 6806.86[b]	104666.67± 1763.83[abcd]

[a] *significant compared with animals in control (NORMAL),*
[b] *significant compared with animals in ulcerated untreated group (UU),*
[c] *significant compared with animals in ulcerated treated with potassium bromate group (UK),*
[d] *significant compared with animals in thyroidectomized ulcerated untreated group (TU),* [e] *significant compared with animals in thyroidectomized ulcerated treated with levothyroxine group (TUT),* [f] *significant compared with animals in thyroidectomized ulcerated treated with potassium bromate group (TUK). Values are expressed as Mean ± SEM and are considered statistically significant when p value < 0.05.*

Table 2
Effect of potassium bromate on white blood cells and differential count in euthyroid and hypothyroid states.

	WBC (× 105 µL)		EOS (%)		LYM (%)		NEUT (%)		MONO (%)		P-L RATIO		N-L RATIO		M-L RATIO	
GRP	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**
NL	3666.67 ± 88.19	5450 ± 132.29	2.00 ± 0.58	2.00 ±0.58	71.0 ± 0.58	70.67 ± 0.67	25± 1	25.67± 0.58	2± 0	1± 0	1983.28± 56.22	2443.50± 127.45	0.35± 0.01	0.36 ± 0	0.03± 0.01	0.01 ±0
UU	5316.67± 187.82a	5733.33± 317.98	1.67± 0.88	2± 0.58	74± 0.58	64.67± 0.88a	22.0 ± 1.73	25.67± 3.06	2 ± 0.58	2± 0.58	1531.74± 70.30	3626.61± 32.78**a**	0.33± 0.03	0.41± 0.04	0.02± 0.00	0.04± 0.00**a**
UK	5216± 148.13a	6916.67± 268.22a	1.33± 0.33	2± 0.58	73± 0.58	74.33± 0.33ab	25 ±1	21± 2ab	1.67± 0.33	2± 0.00	2153.13± 203.39b	3152.68± 113.09**a**	0.33± 0.01	0.30± 0.01 **b**	0.02± 0.00	0.03± 0.00
TU	2983.33± 496.94bc	4966.67± 272.85c	1.67± 0.33	2.67± 0.33	72± 0	68.67± 1.20bc	24.67 ± 2.08	27.0 ± 1.73c	1.67± 0.67	1.67± 0.33	2305.01± 126.94b	2382.31± 238.16**bc**	0.34± 0.02	0.39± 0.02 **c**	0.02± 0.00	0.02± 0.00
TUT	4766.67± 683.943d	4933.33± 404.489c	2 ±0.58	1 ±0.00	71 ± 0.58	74 ± 0.58bd	26 ± 0.00	23 ± 0.00	1.67 ± 0.33	1.67± 0.33	1835.93± 68.29	1617.07± 22.77**abcd**	0.37± 0	0.31± 0**bd**	0.02± 0.00	0.03± 0.00
TUK	4216.67± 145.29	2866.67± 233.33abcde	1.00± 0.00	2.00± 0.00	70.6± 0.88	74.67± 1.45abd	26.33± 0.58b	23 ± 2.00	1.33 ± 0.33	2 ±0.58	2215.5± 145.18b	1429.82± 53.55**abcd**	0.37± 0.01	0.35± 0.02	0.02± 0.00	0.02± 0.01**b**

[a] *significant compared with animals in control (NORMAL),*
[b] *significant compared with animals in ulcerated untreated group (UU),*
[c] *significant compared with animals in ulcerated treated with potassium bromate group (UK),*
[d] *significant compared with animals in thyroidectomized ulcerated untreated group (TU),* [e] *significant compared with animals in thyroidectomized ulcerated treated with levothyroxine group (TUT),* [f] *significant compared with animals in thyroidectomized ulcerated treated with potassium bromate group (TUK). Values are expressed as Mean ± SEM and are considered statistically significant when p value < 0.05.*

Table 3
Erythrocyte sedimentation rate and plasma proteins, electrolytes and lipid profile across thyroidectomised groups

	Esr (Mm/Hr)		Total Protein (G/Dl)		Albumin (G/Dl)		Globulin (G/Dl)		Albumin-Globulin Ratio		Sodium Ion (Mmol/L)		Potassium Ion (Mmol/L)		Chloride Ion (Mmol/L)		Cholesterol (Mg/Dl)		Triglyceride (Mg/Dl)		Hdl (Mg/Dl)		Ldl (Mg/Dl)	
GRP	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**
TU	1.3 ±.06 **a**	0.87 ± 0.07	7.40 ± 0.10	6.63 ± 0.32	2.67 ± 0.03	2.90 ± 0.15 **b**	4.73 ± 0.09	3.73 ± 0.32	0.57 ± 0.03	0.73 ± 0.09 **a**	138 ± 0.58	139 ± 2.08	4.73 ± 0.03	4.67 ± 0.27 **c**	104.33 ± 2.19	108.33 ± 2.73	71.33 ± 1.33	64.33 ± 2.33	43.67 ± 1.76	46.33 ± 0.88	40.67 ± 1.20	33 ± 1.53	21.40 ± 0.31	22.07 ± 1.38
TUT	1.2 ± 0.12 **a**	1 ± 0	7.47 ± 0.20	6.77 ± 0.12	2.93 ± 0.09	2.87± 0.03 **bc**	4.87 ± 0.09	3.73 ± 0.03	0.53 ± 0.03	0.70 ± 7.90E-17	141 ± 1	136.3 ± 0.33 **c**	4.83 ± 0.09	4.67 ± 0.03 **c**	106 ± 3.06	103 ± 0.58 **c**	73 ± 1.73	61.33 ± 0.88	47.33 ± 2.33	42.33 ± 0.88 **b**	43 ± 1.00	31 ± 0.58	21.87 ± 0.74	22.07 ± 0.37
TUK	1.2 ± 0.06 **a**	1.17± 0.09 **abc**	7.73 ± 0.20	6.83 ± 0.13	2.73 ± 0.07	2.90 ± 0.06 **b**	4.80 ± 0.10	3.83 ± 0.03	0.6 ± 0.00	0.70 ± 7.90E-17	138.6± 1.20	138 ± 1.15 **c**	4.50 ± 0.10	4.77 ± 0.09 **c**	108 ± 3.06	110.33 ± 5.24 **a**	70 ± 2.89	63.33 ± 1.20	47 ± 2.52	42.67 ± 1.20	41.33 ± 0.88	35.67 ± 0.33 **be**	22.13 ± 0.64	20.47 ± 0.24

[a] significant compared with animals in control (NORMAL), [b] significant compared with animals in ulcerated untreated group (UU), [c] significant compared with animals in ulcerated treated with potassium bromate group (UK), [d] significant compared with animals in thyroidectomized ulcerated untreated group (TU), [e] significant compared with animals in thyroidectomized ulcerated treated with levothyroxine group (TUT), [f] significant compared with animals in thyroidectomized ulcerated treated with potassium bromate group (TUK). Values are expressed as Mean ± SEM and are considered statistically significant when p value < 0.05.

Table 4:
Effect of potassium bromate on organ weight, renal and hepatic function in euthyroid and hypothyroid states

	Stomach weight		Liver weight		BUN (mg/dL)		CR (mg/dL)		AST (µL)		ALT (µL)		ALP (µL)		TBIL (mg/dL)	
GRP	**Day 3**	**Day 7**	**DAY 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**	**Day 3**	**Day 7**
NL	0.90 ± 0.03	1.09 ± 0.06	4.92 ± 0.32	5.43 ± 0.18	16.40 ± 0.21	16.40 ± 0.21	0.70 ± 7.9E-17	0.70 ± 7.9E-17	40.67± 0.67	40.33± 0.33	31± 0.58	29.33 ± 0.33	103 ± 1.00	80.33 ± 1.45	0.30 ± 0	0.10 ± 9.8E-18
UU	0.98 ± 0.00	0.97 ± 0.05	5.04 ± 0.13	6.76 ± 0.18 **acdef**	16.70 ± 0.06	15.43 ± 0.15**a**	0.80 ± 7.9E-17	0.70 ± 7.9E-17	43 ± 0	38.33 ± 0.33	31.67± 0.33	26 ± 0.58	102.67 ± 1.45	88.67 ± 1.20	0.33 ± 0.03	0.10 ± 9.8E-18
UK	0.74 ± 0.00	1.08 ± 0.03	4.98 ± 0.12	4.89 ± 0.09	16.47 ± 0.03	16.57 ± 0.15**b**	0.80 ± 7.9E-17	0.80 ± 7.9E-17	42.67± 0.33	41.67± 0.33	30 ± 0	27 ± 1.15	96.67 ± 2.67	104.67 ± 0.88 **ab**	0.20 ± 2E-17**ab**	0.20 ± 2E-17 **ab**
TU	1.26 ± 0.09 **c**	1.67 ± 0.22 **abcef**	4.23 ± 0.06	4.81 ± 0.46	16.77 ± 0.15	17.67 ± 0.18	0.60 ± 0**bc**	0.70 ± 0.06	42.33± 0.88	37.33± 1.33 **c**	31 ± 0.58	27 ± 1.15	112 ± 2.08**c**	94.33 ± 5.55 **ac**	0.30 ± 0 **c**	0.23 ± 0.03**ab**
TUT	1.12 ± 0.06 **c**	1.11 ± 0.04	4.43 ± 0.11	4.89 ± 0.19	17.97 ± 0.15	17.47 ± 0.12	0.70 ± 7.9E-17	0.67 ± 0.03**c**	43.67± 0.88	37 ± 0.58 **c**	32 ± 1.15	27 ± 1.15	115 ± 1.15**abc**	111 ± 1.53**abd**	0.40 ± 3.9E-17	0.20 ± 2E-17**ab**
TUK	1.23 ± 0.08 **c**	1.09 ± 0.09	4.57 ± 0.19	5.21 ± 0.58	18.13 ± 0.23	17.43 ± 0.12	0.67 ± 0.03	0.67 ± 0.03**c**	44.33± 1.33	37 ± 1.00**c**	31.33± 0.88	29.67 ± 0.88	120.33 ± 0.88**abc**	106.67 ± 1.76 **abd**	0.30 ± 0	0.27 ± 0.03**ab**

: [a] significant compared with animals in control (NORMAL), [b] significant compared with animals in ulcerated untreated group (UU), [c] significant compared with animals in ulcerated treated with potassium bromate group (UK), [d] significant compared with animals in thyroidectomized ulcerated untreated group (TU), [e] significant compared with animals in thyroidectomized ulcerated treated with levothyroxine group (TUT), [f] significant compared with animals in thyroidectomized ulcerated treated with potassium bromate group (TUK). Values are expressed as Mean ± SEM and are considered statistically significant when p value < 0.05.

Haematological profile, plasma content, renal and hepatic function.: Table 1 shows alterations in haematological parameters during bromate exposure across thyroid states. Packed cell volume (PCV) and red blood cell (RBC) count were reduced, but haemoglobin content in red blood cell relative to the cells volume (Mean corpuscular haemoglobin concentration (MCHC)) was significantly increased in bromate exposed hypothyroid rats by day 3. The values tended towards normal by day 7.

Table 2 depicts white blood cell (WBC) and differential count during bromate exposure across thyroid states, while Table 3 shows no alterations in plasma protein, electrolyte and lipid content during bromate exposure across thyroid states. There was significant increase in plasma chloride but significant decrease in plasma potassium and cholesterol levels in bromate exposed hypothyroid rats by day 3. The values tended towards normal by day 7. Table 4 shows no alterations in renal and hepatic function during bromate exposure across thyroid states.

DISCUSSION

Loss of body weight is an indicator towards pathology or efficacy of a treatment regime during a disease state (Dietze *et al*., 2016). Hypothyroidism has been linked with weight gain in humans and rodents (Carlwe *et al*., 2013; Dale *et al*., 2001). High doses of potassium bromate exposure has been reported to cause a decrease in body weight (Kurokawa *et al*., 1990; Ajarem *et al*., 2016), probably indicative of toxicity while Abuelgasim *et al*., 2008, Dongmei *et al*., 2015; Salami *et al*., 2020) noted no changes in body weight between potassium bromate treated animals and control in euthyroid state. In this study, potassium bromate (at a low dose) increased body weight in euthyroid animals but not in hypothyroid animals. These variations in body weight (increase or decrease) might be due to dosage exposure, a high dose of potassium bromate is indicative of toxicity hence loss of body weight while low dose exposure might be beneficial to the system.

Hypothyroidism has been linked with a prolonged proliferative phase of wound healing (Cannon, 1994; Thá Nassif *et al*., 2009). In this study thyroidectomised animals treated with thyroxine had the highest percentage inhibition ulcer score which is similar to observations of other studies (Oluwole and Saka, 2007; Adeniyi *et al*., 2014; Salami *et al*., 2016). Potassium bromate greatly reduced the mean ulcer score in thyroidectomised ulcerated rats. Bromide ion (from reduction of bromate in vivo) has been shown to replace iodine in the thyroid forming brominated analogues of thyroid hormone (Velicky *et al*., 1998; Pavelka, 2004) mimicking the functions of iodine more (Vobecky *et al*., 1996). However, in a recent study, cadexomer iodine has been documented to reduce ulcer size and facilitate complete healing of wounds (Raju *et al*., 2019, Gupta *et al*., 2022). It may be that in the absence of thyroid hormone synthesis in the thyroid gland, bromide ion mimicks the action of iodine and release of thyroid stimulating hormone (Allain and MacGregor, 1993) thus bringing about ulcer healing. Thus it is safe to conclude that a normal level of thyroxine is required for optimal healing of gastric ulcer.

Hypothyroidism predisposes to a drastic reduction in the pace of metabolic processes, leading to metabolic anomalies like anaemia. In fact, about half of hypothyroid patients present with at least one type of anaemia (Bashir *et al*., 2012; Shah *et al*., 1999). In the same vein, potassium bromate has been shown to elicit in vitro erythrocytic lysis and a diagnosis of anaemia in humans (Ahmad *et al*., 2014; SONG *et al*., 2001, Omer *et al*., 2008; Stuti and D'Souza, 2013; Altoom *et al*., 2017). However, in this study it was observed that potassium bromate prevented anemia by maintaining RBC, PCV, Hb and reticulocyte values similar to that of normal animals in non-thyroidectomised animals. This is similar to the findings of Kurokawa *et al*., (1990) and Achukwu *et al*., (2009). However in thyroidectomised animals, potassium bromate did not prevent anemia as RBC, PCV and Hb values were decreased, which leads us to infer that the decrease was as a result of ulceration rather than treatment of bromate.

Though previous studies noted a decrease in white blood cells (WBC) when potassium bromate was administered (Achukwu *et al*., 2009; Altoom *et al*., 2017), while the bromate treated rats had decreased WBC count. Potassium bromate increased lymphocyte count in both thyroidectomised and non-thyroidectomised animals. Inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to- lymphocyte ratio (PLR), or Monocyte-to-lymphocyte ratio (MLR), have been used as markers in the assessment of disease activity in gastric ulcer (Adeniyi *et al*., 2018) and inflammatory bowel disease (IBD) (Erademir *et al*., 2016). Nitric Oxide – Malondialdehyde ratio (NO/MDA) may be considered as an integrated marker of degree of inflammation and lipid peroxidation (Caimi *et al*., 2014) in tissues. NO/MDA is low when there is more inflammation compared to vasodilation. NO/MDA is high when there is more vasodilation than inflammation. NO has been shown to decrease mitochondrial MDA content (He *et al*., 2019). Potassium bromate treated animals had NO/MDA ratios similar to that of normal animals even in the presence or absence of the thyroid gland. This suggests that potassium bromate at the administered dose modulated inflammatory response in ulcerated animals both in the presence or absence of the thyroid gland.

Erythrocyte sedimentation rate (ESR), plasma viscosity and fibrinogen are less predictive markers of inflammation in diseased conditions like gastric ulceration (Salami *et al*., 2017). Potassium bromate increased ESR in non-thyroidectomised animals but it was decreased in thyroidectomised animals. The increase in ESR of animals with intact thyroid may have been as a result of inflammation resulting from ulceration (Bridgen, 1999). The decrease noted in thyroidectomised animals may have been due to plasma protein abnormalities (Bridgen, 1999) since decrease in thyroid hormones affects plasma protein synthesis (Graninger *et al*., 1986). Fibrinogen, an inflammatory marker and a major coagulation protein in the blood, has been found to be increased in patients with diabetic foot ulcer (Li *et al*., 2016). Fibrinogen levels were normal in potassium bromate treated rats. Lower serum albumin levels has been shown to delay peptic ulcer healing and cause peptic ulcer bleeding (PUB) and other complications (Hu *et al*., 2017; Cheng *et al*., 2018). Potassium bromate increased albumin levels in animals with intact thyroid gland which contradicts reports of lowered albumin and serum protein levels in potassium bromate treated animals (Omer *et al*., 2008; Stuti and D'Souza,

2013); while a general decrease was observed in all thyroidectomized ulcerated rats at day 3 which reverted back to normal by day 7.

In this study, animals with intact thyroid gland treated with potassium bromate had high sodium, potassium and chloride ions. The thyroidectomised potassium bromate treated ulcerated animals with had normal electrolyte levels. Kurokawa *et al*., (1990) reported increased sodium levels and decreased potassium levels, while Abuelgasim *et al*., (2008) reported the inverse in potassium bromate treated animals. The increased chloride may have been as a result of bromide ion displacing body chloride (Pavelka, 2004).

Changes in their activities of Aspartate aminotransferase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP) are indicative of liver damage by toxicants or in disease conditions (Oseni *et al*., 2018). The AST and ALT levels were normal in potassium bromate treated animals with or without the thyroid gland indicating absence of liver toxicity. This contradicts several studies done on potassium bromate which reported liver toxicity and increased AST and ALT in animals treated with potassium bromate (Omer *et al*., 2008; Oloyede and Sunmonu, 2009; Oseni *et al*., 2015; Oseni *et al*., 2018). This may be because the dose of potassium bromate administered in this study is much lower than that used in the other studies which ranged from 30 to 200 mg/kg. Increased ALP has been associated with growth spurts (Shipman, 2013) which was evident in these groups. Blood urea nitrogen and creatinine levels which are used to evaluate kidney function were normal for both thyroidectomised and normal ulcerated animals treated with potassium bromate. This means that potassium bromate had no adverse effect on kidney function and is in line with DeAngelo *et al*., (1998) and Abuelgasim *et al*., (2008).

Increased lipid peroxidation has been reported to contribute to mucosal inflammation (Biswas *et al*., 2003; Omayone *et al*., 2016). Malondialdehyde (MDA) level has been shown to be elevated in potassium bromate treated animals (Josiah *et al*., 2011; Josiah *et al*., 2012; Oseni *et al*., 2015; Ahmad *et al*., 2015; Oseni *et al*., 2018). This study observed that non-thyroidectomised rats treated with potassium bromate had lower gastric MDA levels (unlike in the ulcer untreated group), while thyroidectomised rats had minimal peroxidation. However, liver of potassium bromate treated rats showed elevated MDA levels by day 7.

Increased protein carbonyl levels have been found in the intestine of animals treated with potassium bromate (Ahmad *et al*., 2015). However, it had no such effect on thyroidectomised animals as elevated carbonyl levels were observed in all the treatment groups by day 7. The reason for this may be the oxidative stress known to be associated with thyroidectomy and ulceration (Salami *et al*., 2016).

Endogenous antioxidants (Superoxide dismutase (SOD), catalase and Sulfhydryl) have been reported to be decreased in gastric ulcer, as a result of increased lipid peroxidation (Omayone *et al*., 2016). However, potassium bromate protected against tissue damage from oxidative stress in both normal and thyroidectomised animals in this study contrary to earlier reports (Oseni *et al*., 2015; Silva *et al*., 2015; Costa *et al*., 2019).

In contrast, the thyroid hormones play crucial roles in the wound healing process, including enhancing collagen formation, mitochondrial oxidative phosphorylation, inducing protein synthesis, and diminishing fibroblast function (Kivirikko *et al*., 1967; Natori *et al*., 1999; Sterling, 2010). This explains the increased gastric mucin content that we found in the thyroxine treated group, as adequate mucin production is important for the protection of gastric epithelial layers from perturbations like gastric acid secretion (Adeniyi *et al*., 2018; Bansil and Turner, 2006; Salami *et al*., 2021). This study observed an increased mucin content in ulcerated animals treated with potassium bromate both in the thyroidectomised and non-thyroidectomised states.

Nitric oxide production under normal physiological conditions mediates many aspects of inflammation but in abnormal conditions, it is regarded as pro-inflammatory mediator that induces inflammation due to its excess production (Odukanmi *et al*., 2017). This may explain why in the non-thyroidectomised animals, the ulcer untreated group had the highest nitric oxide level at both days 3 and 7, probably due to ulcer formation. Potassium bromate did not alter nitric oxide levels in both non-thyroidectomised and thyroidectomised animals.

The sodium potassium pump helps in maintaining resting membrane potential and controlling the intracellular ion concentration inside the cell, which are important for numerous of the cell's enzymatic functions (Sherwood, 2012; Clausen *et al*., 2017). The thyroid hormone influences metabolic energy generation via enhanced mitochondrial function for Adenosine triphosphate (ATP) production (Harper and Seifert, 2008). Consequently, similar patterns of recovery from toxin-related injury have been recorded in thyroxine-treated rats and their ATP-MgCl2 treated counterparts (Siegel *et al*., 1984). Given that tissue repair is energy-intensive (Schulte-Wissermann *et al*., 1977), we investigated how different thyroid states affect gastric ulcer healing during low oral dose bromate exposure. This study observed that potassium bromate increased gastric sodium potassium pump activity in non-thryoidectomised ulcerated rats while it maintained pump activity within normal range in thyroidectomised animals.

Previous study Salami *et al*., 2020, documented that Protocatechuic acid ameliorated gastric ulceration during potassium bromate exposure at a low dose however, similar activities of increased antioxidant status, gastric sodium potassium pump activities and angiogenesis in the bromate treated groups were also observed in this study. This observation needs critical evaluation as both studies reveals angiogenesis, increased gastric sodium potassium pump activities and antioxidant activities at the dose of potassium bromate administered.

In conclusion, this study showed that in the absence or decrease of the thyroid hormones, low-dose potassium bromate mimicks the effect of thyroxine thereby promoting gastric ulcer healing. Potassium bromate at low dose prevented anemia associated with ulcer contrary to reports of anemia after treatment with high doses of potassium bromate. From the results of our study, low dose potassium bromate was found to be gastroprotective in both non-thyroidectomised and thyroidectomised states and had no toxic effect on the liver or blood, unlike reports of toxicity at high doses.

REFERENCES

Abuelgasim, A.I., Omer, R., and Elmahdi, B. (2008): Serrobiochemical Effects of Potassium Bromate on Wistar

Albino Rats. *American Journal of Food Technology* 3(5): 303-309

Achukwu, P.U., Ufelle, S.A., Ukaejiofo, E.O., Ejezie, F.E., Nwachukwu, D.N., Nwagha, U.I, Nworie, W.C, and Anyaehie, U.S.B. (2009): The Effect of Potassium Bromate on some Haematological Parameters of Wistar Rats. *Nigerian Journal of Physiological Sciences* 24 (1): 59 – 61

Adeniyi, O.S., Emikpe, B.O., and Olaleye, S.B. (2014): Gastric Mucosa Re-epithelisation, Oxidative Stress and Apoptosis during Healing of Acetic Acid-Induced Ulcerations in Thyroxine Treatment and Thyroidectomy on Rats. *J. Afr. Ass. Physiol. Sci.* 2 (1): 57-67.

Adeniyi, O.S., Emikpe, B.O., and Olaleye, S.B. (2018). Accelerated gastric ulcer healing in thyroxine-treated rats: roles of gastric acid, mucus, and inflammatory response. https://doi.org/10.1139/cjpp-2017-0399 96, 597–602. https://doi.org/10.1139/CJPP-2017-0399

Ahmad, M.K., Amani, S., and Mahmood, R. (2014). Potassium bromate causes cell lysis and induces oxidative stress in human erythrocytes. *Environ Toxicol* 29, 138–145. https://doi.org/10.1002/TOX.20780

Ahmad, M.K., Khan, A.A., Ali, S.N., and Mahmood, R. (2015): Chemoprotective Effect of Taurine on Potassium Bromate-Induced DNA Damage, DNA Protein Cross-Linking and Oxidative Stress in Rat Intestine. *PLoS ONE* 10(3): e0119137. doi:10.1371/journal.pone.0119137

Ajarem, J., Altoom, N.G., Allam, A.A, Maodaa, S.N, Abdel-Maksoud, M.A., and Chow, B.K.C. (2016): Oral administration of potassium bromate induces neurobehavioral changes, alters cerebral neurotransmitters level and impairs brain tissue of swiss mice. *Behav Brain Funct* 12:14. DOI 10.1186/s12993-016-0098-8

Akpamu, U., Otamere, H.O., Ernest-Nwoke, I. O., Ekhator, C. N., Osifo, U.C. (2016). The protective effect of testosterone on Indomethacin induced gastric ulcer in female Sprague Dawley rats. *Advances in Endocrinology*, 2016, Article ID 3452760, 5 pages. https://doi.org/10.1155/2016/3452760

Allain, T. J., and McGregor, A. M. (1993). Thyroid hormones and bone. *Journal of Endocrinology*, 139(1), 9-18.

Al-Mareed, A.A., Farah, M.A., Al-Anazi, K.M., Hailan, W.A.Q., and Ali, M.A., (2022). Potassium bromate-induced oxidative stress, genotoxicity and cytotoxicity in the blood and liver cells of mice. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis* 878, 503481. https://doi.org/10.1016/J.MRGENTOX.2022.503481

Altoom, N.G., Ajarem, J., Allam, A.A., Maodaa, S.N., and Abdel-Maksoud, M.A., (2018). Deleterious effects of potassium bromate administration on renal and hepatic tissues of Swiss mice. *Saudi J Biol Sci* 25, 278–284. https://doi.org/10.1016/J.SJBS.2017.01.060

Bansil, R., and Turner, B.S., (2006). Mucin structure, aggregation, physiological functions and biomedical applications. *Curr Opin Colloid Interface Sci* 11, 164–170. https://doi.org/10.1016/J.COCIS.2005.11.001

Bashir, H., Bhat, M.H., Farooq, R., Majid, S., Shoib, S., Hamid, R., Mattoo, A.A., Rashid, T., Bhat, A.A., Wani, H.A., and Masood, A. (2012). Comparison of hematological parameters in untreated and treated subclinical hypothyroidism and primary hypothyroidism patients. *Med J Islam Repub Iran* 26, 172.

Batista, L.M., Lima, G.R.D.M., De Almeida, A.B.A. *et al*. (2015) Ulcer healing and mechanism(s) of action involved in the gastroprotective activity of fractions obtained from Syngonanthus arthrotrichus and Syngonanthus bisulcatus. *BMC Complement Altern Med* 15, 391 https://doi.org/10.1186/s12906-015-0923-x

Beckert, S., Class, N., Farrahi, F., and Coerper, S. (2004). Growth hormone enhances gastric ulcer healing in rats. Med Sci Monit. 10(8):BR255-8. *Epub* 2004 Jul 23. PMID: 15277985.)

Bewaji, C.O., Olorunsogo, O.O., and Bababunmi, E.A. (1985). Comparison of the membrane-bound (Ca2+ + Mg2+)-ATPase in erythrocyte ghosts from some mammalian species. *Comparative Biochemistry and Physiology -- Part B: Biochemistry* and 82, 117–122. https://doi.org/10.1016/0305-0491(85)90138-5

Bhattacharyya, A., Chattopadhyay, R., Mitra, S., and Crowe, S.E. (2014). Oxidative Stress: An Essential Factor in the Pathogenesis of Gastrointestinal Mucosal Diseases. *Physiol Rev* 94, 329. https://doi.org/10.1152/PHYSREV.00040.2012

Biswas, K., Bandyopadhyay, U., Chattopadhyay, I., Varadaraj, A., Ali, E., and Banerjee, R.K. (2003): Mechanism of antiulcer effect of omeprazole. *The American Society for Biochemistry and Molecular Biology*, Manuscript M210328200

Bonacquisti, T.P. (2006). A drinking water utility's perspective on bromide, bromate, and ozonation. Toxicology 221, 145–148. https://doi.org/10.1016/J.TOX.2006.02.010

Brecher, G., and Cronkite, E.P. (1950). Morphology and Enumeration of Human Blood Platelets. https://doi.org/10.1152/jappl.1950.3.6.365 3, 365–377. https://doi.org/10.1152/JAPPL.1950.3.6.365

Brent, G.A. (2012). Mechanisms of thyroid hormone action. J Clin Invest 122, 3035–3043. https://doi.org/10.1172/JCI60047

Bridgen, M.L. (1999): Clinical utility of the erythrocyte sedimentation rate. *Am. Fam. Physician*; 60(5): 1443-50

Bromate CASRN 15541-45-4 | IRIS | US EPA, ORD [WWW Document], n.d. URL https://iris.epa.gov/ChemicalLanding/&substance_nmbr=1002 (accessed 4.23.23).

Burstein, C. (2007). Hematology: Clinical principles and applications. LaboratoriumsMedizin 31, 278–279. https://doi.org/10.1515/JLM.2007.040

Cannon, C.R. (1994). Hypothyroidism in head and neck cancer patients: Experimental and clinical observations. Laryngoscope 104, 1–21. https://doi.org/10.1288/00005537-199411001-00001

Caimi, G., Presti, R.L., Montana, M., Noto, D., Canino, B., Averna, M.R., and Hopps, E. (2014): Lipid peroxidation, nitric oxide metabolites, and their ratio in a group of subjects with metabolic syndrome. *Oxidative Medicine and Cellular Longevity;* Volume 2014, Article ID 824756, 8 pages

Carlwe, M., Schaffer, T., and Sjöberg, S. (2013). Short-term Withdrawal of Levothyroxine, Induced Increase of Thyroid-stimulating Hormone and an Increase Ratio of Triiodothyronine to Thyroxine. *Eur Endocrinol* 9, 37. https://doi.org/10.17925/EE.2013.09.01.37

Cheng, S.Y., Leonard, J.L., and Davis, P.J. (2010). Molecular aspects of thyroid hormone actions. *Endocr Rev* 31, 139–170. https://doi.org/10.1210/ER.2009-0007

Chipman, J.K., Davies, J.E., Parsons, J.L., Nair, J., O'Neill, G., and Fawell, J.K. (1998). DNA oxidation by potassium bromate; a direct mechanism or linked to lipid peroxidation? Toxicology 126, 93–102. https://doi.org/10.1016/S0300-483X(97)00174-1

Christ-Crain, M., Huber, P.R., Keller, U., Meier, C., Müller, B., Puder, J., and Staub, J.-J. (2004). Changes in Liver Function correlate with the Improvement of Lipid Profile after Restoration of Euthyroidism in Patients with Subclinical Hypothyroidism. *EXCLI J* 3, 1–9. https://doi.org/10.17877/DE290R-14916

Claiborne, A. (1985). Catalase activity, in: Handbook of Methods for Oxygen Radical Research. CRC Press, Boca Raton, pp. 283–284.

Clausen, M.V., Hilbers, F. and Poulsen, H. (2017): The structure and function of the Na,K-ATPase isoforms in health and disease. *Frontiers in Physiology*; 8:371

Costa, P., Somensi, L.B., Silva, R.C.S., Mariano, L.N.B., Boeing, T., Longo, B., Perfoll, E., Souza, P., Gushiken, L.F.S., Pellizzon, C.H., Rodrigues, D.M., Bastos, J.K., Andrade, S.F., and Silva, L.M. (2019): Role of the antioxidant properties in the gastroprotective and gastric healing activity promoted by Brazilian green propolis and the healing efficacy of Artepillin C. *Inflammopharmacology.* DOI: https://doi.org/10.1007/s10787-019-00649-7

Dale, J., Daykin, J., Holder, R., Sheppard, M.C., and Franklyn, J.A. (2001). Weight gain following treatment of hyperthyroidism. *Clin Endocrinol* (Oxf) 55, 233–239. https://doi.org/10.1046/J.1365-2265.2001.01329.X

Das, K., and Chainy, G.B.N. (2001). Modulation of rat liver mitochondrial antioxidant defence system by thyroid hormone. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease 1537, 1–13. https://doi.org/10.1016/S0925-4439(01)00048-5

Deangelo, A.B., George, M.H., Kilburn, S.R., Moore, T.M., and Wolf, D.C. (1998)

. Carcinogenicity of Potassium Bromate Administered in the Drinking Water to Male B6C3F, Mice and F344/N Rats*. Safety Assessment TOXICOLOGIC PATHOLOGY 26, 587–594.

Dietze, S., Lees, K.R., and Voigt, J. (2016): Food deprivation, body weight loss and anxiety-related behavior in rats. Animals (Basel). 6(1): 4.

Dongmei, L., Zhiwei, W., Qi, Z., Fuyi, C., Yujuan, S., and Xiaodong, L. (2015). Drinking water toxicity study of the environmental contaminant—Bromate. Regulatory Toxicology and Pharmacology 73, 802–810. https://doi.org/10.1016/J.YRTPH.2015.10.015

Elinder, C.G., Edling, C., Lindberg, E., Kågedal, B., and Vesterberg, O. (1985). Assessment of renal function in workers previously exposed to cadmium. *Occup Environ Med* 42, 754–760. https://doi.org/10.1136/OEM.42.11.754

Ellman, G.L. (1959). Tissue sulfhydryl groups. *Arch Biochem Biophys* 82, 70–77. https://doi.org/10.1016/0003-9861(59)90090-6

Erion, M.D., Cable, E.E., Ito, B.R., Jiang, H., Fujitaki, J.M., Finn, P.D., Zhang, B.H., Hou, J., Boyer, S.H., Van Poelje, P.D., and Linemeyer, D.L. (2007). Targeting thyroid hormone receptor-β agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index. *Proc Natl Acad* Sci U S A 104, 15490–15495. https://doi.org/10.1073/PNAS.0702759104/SUPPL_FILE/02759SUPPAPPENDIX.PDF

Fagundes, F.L., Piffer, G.d.M., Périco, L.L., Rodrigues, V.P., Hiruma-Lima, C.A., dos Santos, R.d.C., (2020) Chrysin Modulates Genes Related to Inflammation, Tissue Remodeling, and Cell Proliferation in the Gastric Ulcer Healing. International *Journal of Molecular Sciences*. 21(3):760. https://doi.org/10.3390/ijms21030760

Graninger, W., Pirich, K.R., Speiser, W., Deutsch, E., and Waldhäusl, W.K. (1986): Effect of Thyroid Hormones on Plasma Protein Concentrations in Man. *The Journal of Clinical Endocrinology & Metabolism*, Volume 63, Issue 2, Pages 407–411, https://doi.org/10.1210/jcem-63-2-407

Gornall, A., Bardawill, M., and David, M. (1949). Determination of serum proteins by means of the biuret reaction. *J. Biol. Chem* 177, :751-66.

Gradus (Ben-Ezer), D., Rhoads, M., Bergstrom, L.B., and Jordan, S.C. (1984). Acute Bromate Poisoning Associated with Renal Failure and Deafness Presenting as Hemolytic Uremic Syndrome. *Am J Nephrol* 4, 188–191. https://doi.org/10.1159/000166804

Grasselli, E., Voci, A., Canesi, L., De Matteis, R., Goglia, F., Cioffi, F., Fugassa, E., Gallo, G., and Vergani, L., (2011). Direct effects of iodothyronines on excess fat storage in rat hepatocytes. *J Hepatol* 54, 1230–1236. https://doi.org/10.1016/J.JHEP.2010.09.027

Gredilla, R., Barja, G., and López-Torres, M. (2009). Thyroid hormone-induced oxidative damage on lipids, glutathione and DNA in the mouse heart. https://doi.org/10.1080/10715760100300931 35, 417–425. https://doi.org/10.1080/10715760100300931

Gregor, A., Kostrzewska, E., and Godorowska, W. (1977). Determination of Serum Proteins in the Presence of Dextran by means of the Biuret Reaction. *Transfusion Medicine and Hemotherapy* 4, 48–50. https://doi.org/10.1159/000219790

Gupta, S., Shinde, R. K., and Shinde, S. (2022). Comparison of the outcomes of cadexomer iodine and povidone-iodine ointments in wound management. Cureus, 14(5).

Hampton, D.D., and Hale, L.P (2011). Mast Cells Are Critical for Protection against Peptic Ulcers Induced by the NSAID Piroxicam. *PLoS ONE* 6(8): e23669. https://doi.org/10.1371/journal.pone.0023669

Harper, M.E., and Seifert, E.L. (2008). Thyroid hormone effects on mitochondrial energetics. Thyroid 18, 145–156. https://doi.org/10.1089/THY.2007.0250

He, W., An, X., Li, L., Shao, X., Li, Q., Yao, Q., and Zhang, J.A. (2017). Relationship between Hypothyroidism and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. *Front Endocrinol* (Lausanne) 8, 335. https://doi.org/10.3389/FENDO.2017.00335/BIBTEX

Ignarro, L.J., Buga, G.M., Wood, K.S., Byrns, R.E., and Chaudhuri, G. (1987). Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc *Natl Acad Sci* U S A 84, 9265–9269. https://doi.org/10.1073/pnas.84.24.9265

Josiah, S.J., Nwangwu, S.C.O., Akintola, A.A., Allu, T., Usunobun, U., Njoya, H., and Adejumo, B.I (2011): The Protective Effect of Ethanolic Extract of Unripe Pulp of Carica papaya (Pawpaw) Against Potassium Bromate Induced Tissue Damage in Wistar Rats. *Current Research Journal of Biological Sciences* 3(6): 597-600

Kebapcilar, L., Akinci, B., Bayraktar, F., Comlekci, A., Solak, A., Demir, T., Yener, S., Küme, T., and Yesil, S. (2007). Plasma thiobarbituric acid-reactive substance levels in subclinical hypothyroidism. *Medical Principles and Practice* 16, 432–436. https://doi.org/10.1159/000107747

Khalefa, A. A., Abd-Alaleem, D. I., and Attiaa, K. I. (2010). The protective effects of ghrelin and leptin against stress-induced gastric ulcer in rats. *Arab Journal of Gastroenterology*, 11(2), 74-78. https://doi.org/10.1016/j.ajg.2010.04.005

Kivirikko, K.I., Laitinen, O., Aer, J., and Halme, J. (1967). Metabolism of collagen in experimental hyperthyroidism and hypothyroidism in the rat. *Endocrinology* 80, 1051–1061. https://doi.org/10.1210/endo-80-6-1051

Köroğlu, E., Canbakan, B., Atay, K., Hatemi, İ., Tuncer, M., Dobrucalı, A., Sonsuz, A., Gültepe, İ., and Şentürk, H. (2016). Role of oxidative stress and insulin resistance in disease severity of non-alcoholic fatty liver disease. *Turk J Gastroenterol* 27, 361–367. https://doi.org/10.5152/tjg.2016.16106

Kumar, S., and Pankaj, P. (2012). Accidental Potassium Bromate Poisoning in Nine Adults. *Journal of Indian Academy of Forensic Medicine* 34.

Kunchandy, J., Khanna, S., and Kulkarni, S.K. (1985). Effect of alpha2 agonists clonidine, guanfacine and B-HT 920 on gastric acid secretion and ulcers in rats. *Arch Int Pharmacodyn Ther* 275, 123–138.

Kurokawa, Y., Maekawa, A., Takahashi, M., and Hayashi, Y. (1990). Toxicity and carcinogenicity of potassium bromate - A new renal carcinogen. *Environ Health Perspect* 87, 309–335. https://doi.org/10.1289/EHP.9087309

Levine, R.L., Garland, D., Oliver, C.N., Amici, A., Climent, I., Lenz, A.G., Ahn, B.W., Shaltiel, S., and Stadtman, E.R. (1990). [49] Determination of carbonyl content in oxidatively modified proteins. *Methods Enzymol* 186, 464–478. https://doi.org/10.1016/0076-6879(90)86141-H

Lu, S.C. (2009). Regulation of glutathione synthesis. Mol Aspects Med 30, 42–59. https://doi.org/10.1016/j.mam.2008.05.005

Machowska, A., Szlachcic, A., Pawlik, M., Brzozowski, T., Konturek, S.J., and Pawlik, W.W. (2004). The role of female and male sex hormones in the healing process of preexisting lingual and gastric ulcerations. *J Physiol Pharmacol.55 Suppl* 2:91-104. PMID: 15608364.

Mandato, C., D'Acunzo, I., and Vajro, P. (2018). Thyroid dysfunction and its role as a risk factor for non-alcoholic fatty liver disease: What's new. *Digestive and Liver Disease* 50, 1163–1165. https://doi.org/10.1016/j.dld.2018.08.026

Mantovani, A., Nascimbeni, F., Lonardo, A., Zoppini, G., Bonora, E., Mantzoros, C.S., and Targher, G., (2018). Association between Primary Hypothyroidism and Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Thyroid* 28, 1270–1284. https://doi.org/10.1089/THY.2018.0257/ASSET/IMAGES/LARGE/FIGURE3.JPEG

Matsumoto, I., Morizono, T., and Paparella, M.M. (1980). Hearing Loss following Potassium Bromate: Two Case Reports. Otolaryngology–Head and Neck Surgery 88, 625–629. https://doi.org/10.1177/019459988008800519

Misra, H.P., and Fridovich, I. (1972). The Role of Superoxide Anion in the Autoxidation of Epinephrine and a Simple Assay for Superoxide Dismutase. *J Biol Chem* 247, 3170–3175.

Miyake, T., Suzaki, T., and Oishi, M. (1980): Correlation of gastric ulcer healing features by endoscopy, stereoscopic microscopy, and histology, and a reclassification of the epithelial regenerative process. *Dig Dis Sci*. 25(1):8-14. doi: 10.1007/BF01312726. PMID: 7353454.

Namulema, J., Nansunga, M., Kato, C.D. *et al*. (2018). Thyroid hormones increase stomach goblet cell numbers and mucin expression during indomethacin induced ulcer healing in Wistar rats. Thyroid Res 11, 6. https://doi.org/10.1186/s13044-018-0050-0

Natori, J., Shimizu, K., Nagahama, M., and Tanaka, S. (1999). The influence of hypothyroidism on wound healing An experimental study. Journal of Nippon Medical School 66, 176–180. https://doi.org/10.1272/JNMS.66.176

Nogueira, L., Sanches, A.L.M., da Silva, D.G.H., Ferrizi, V.C., Moreira, A.B., and de Almeida, E.A. (2011). Biochemical biomarkers in Nile tilapia (Oreochromis niloticus) after short-term exposure to diesel oil, pure biodiesel and biodiesel blends. Chemosphere 85, 97–105. https://doi.org/10.1016/J.CHEMOSPHERE.2011.05.037

Odukanmi, O.A., Salami, A.T., Ashaolu, O.P., Adegoke, A.G., and Olaleye, S.B. (2017): Kolaviron attenuates ischemia-reperfusion injury in the stomach of rats. *Appl. Physiol. Nutr. Metab*. 43(1):30-37. doi: 10.1139/apnm-2017-0138. Epub 2017 Aug 25. PMID: 28841395.

Oliveira, M., Pacheco, M., and Santos, M.A. (2008). Organ specific antioxidant responses in golden grey mullet (Liza aurata) following a short-term exposure to phenanthrene. *Science of The Total Environment* 396, 70–78. https://doi.org/10.1016/J.SCITOTENV.2008.02.012

Oluwole, S.O and Saka, M.T. (2007): Effect of thyroid hormone on gastric mucous secretion around indomethacin-induced gastric ulcers in rats. *J Med Sci* 7(4): 678-681.

Omayone, T.P., Salami, A.T., Oluwole, F.S. and Olaleye, S.B. (2016): Gastroprotective effect of vanadium in rats - the roles of gastric acid and nitric oxide. *J. Afr. Ass. Physiol. Sci*. 4 (1): 32-40

Omer, R., Abuelgasim, A.I., and Elmahdi, B. (2008): Effect of Potassium Bromate on Liver and Blood Constituents of Wistar Albino Rats. *American Journal of Food Technology*, 3: 310-314.

Oseni, O. A., Ogunmoyole T., and Idowu K. A. (2015): Lipid Profile and Cardio-Protective Effects of Aqueous Extract of Moringa Oleifera (Lam) Leaf on Bromate- Induced Cardiotoxicity on Wistar Albino Rats. *European Journal of Advanced Research in Biological and Life Sciences* Vol. 3 (2)

Pagadala, M.R., Zein, C.O., Dasarathy, S., Yerian, L.M., Lopez, R., and McCullough, A.J. (2012). Prevalence of hypothyroidism in nonalcoholic fatty liver disease. *Dig Dis Sci* 57, 528–534. https://doi.org/10.1007/S10620-011-2006-2/METRICS

Post, H., Hundt, J.E., Zhang, G., Depping, R., Rose, C., Langan, E.A., and Paus, R. (2021). Thyroxine restores severely impaired cutaneous re-epithelialisation and angiogenesis in a novel preclinical assay for studying human skin wound healing under "pathological" conditions ex vivo. Arch Dermatol Res 313, 181–192. https://doi.org/10.1007/S00403-020-02092-Z/FIGURES/4

Raju, R., Kethavath, S.N., Sangavarapu, S.M., and Kanjarla, P. (2019). Efficacy of cadexomer iodine in the treatment of chronic ulcers: A randomized, multicenter, controlled trial.Wounds 31 85–90.

Recknagel, R.O., Glende, E.A., and Britton, R.S. (2020). Free Radical Damage and Lipid Peroxidation. *Hepatotoxicology* 401–436. https://doi.org/10.1201/9780367812041-9

Rowan, R.M. (1983). Blood Cell Volume Analysis: A New Screening Technology for the Haematologist., in: Albert Clark.

Salami, A.T., Odukanmi, O.A., Olagoke, C.O., Iyiola, T.O., and Olaleye, S.B. (2016). Role of nitric oxide and endogenous antioxidants in thyroxine facilitated healing of ischemia-reperfusion induced gastric ulcers. *Nigerian Journal of Pharmaceutical Research* 12, 189–206. https://doi.org/10.4314/njpr.v12i2.

Salami A.T., Odukanmi O. A., Faniyan O. F., Omayone T.P., and Olaleye S. B. (2017): Seeds of Buchholzia coriacea in Diet Mitigate Ischemic Reperfusion–Induced Gastric Ulceration in Experimental Rats, *Journal of Dietary Supplements*, DOI: 10.1080/19390211.2017.1404544

Salami, A.T., Adebimpe, M.A., Olagoke, O.C., Iyiola, T.O., and Olaleye, S.B., (2020). Potassium bromate cytotoxicity in the Wister rat model of chronic gastric ulcers: Possible reversal by protocatechuic acid. *J Food Biochem* 44(12), e13501. https://doi.org/10.1111/JFBC.13501

Salami, A.T., Okonkwo, C.E., Attah, F.A., and Olagoke, O.C., (2021). Bioactive Moringa olifera seed extracts attenuates cholesterol gall stones in hyperglycaemic Swiss mice. *Comparative Clinical Pathology*, 30(2), 207–216. https://doi.org/10.1007/S00580-021-03206-3

Salami, A.T., Odukanmi, A.O., Adeola A., Iyiola T.O. and Olaleye S.B (2021). Artesunate, with or without Mefloquine, alters activities of Mast cells, Anti-inflammatory markers and Antioxidants in Rats with Acetic acid induced Gastric ulcers. *Arch. Bas. App. Med*. 9 (2021): 45– 57.

Schulte-Wissermann, H., Straub, E., and Funke, P.J. (1977). Influence of L-thyroxine upon enzymatic activity in the renal tubular epithelium of the rat under normal conditions and in mercury-induced lesions. I. Histochemical studies of alkaline phosphatase, acid phosphatase, adenosine- tri-phosphatase and leucine-aminopeptidase. *Virchows Arch B Cell Pathol* 23, 163–173. https://doi.org/10.1007/BF02889128

Sedlak, J., and Lindsay, R.H. (1968). Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. *Anal Biochem* 25, 192–205. https://doi.org/10.1016/0003-2697(68)90092-4

Senese, R., Cioffi, F., de Lange, P., Leanza, C., Iannucci, L.F., Silvestri, E., Moreno, M., Lombardi, A., Goglia, F., and Lanni, A. (2017). Both 3,5-diiodo-L-thyronine and 3,5,3'-triiodo-L-thyronine prevent short-term hepatic lipid accumulation via distinct mechanisms in rats being fed a high-fat diet. *Front Physiol* 8, 706. https://doi.org/10.3389/FPHYS.2017.00706/BIBTEX

Shah, S., Begum, M., Akter, D.M., Rahman, A.A.T.M., Uddin, F., and Rahman, J. (1999). [Anemia in hypothyroidism]. *Med Pregl* 52, 136–140. https://doi.org/10.3329/bmrcb.v46i1.47470

Shahid, M.A., Ashraf, M.A., and Sharma, S. (2022). Physiology, Thyroid Hormone. StatPearls.

Sherwood L. (2012): The digestive system. Fundamentals of Human Physiology. 4th Edition.

Shu, W., Yang, M., Yang, J., Lin, S., Wei, X., and Xu, X. (2022). Cellular crosstalk during liver regeneration: unity in diversity. *Cell Communication and Signaling* 2022 20:1 20, 1–13. https://doi.org/10.1186/S12964-022-00918-Z

Si, M., Cao, Q., and Wu, G. (2005). Quality of gastric ulcer healing evaluated by endoscopic ultrasonography. *World Journal of Gastroenterology* : WJG, 11(22), 3461-3464. https://doi.org/10.3748/wjg.v11.i22.346;

Siegel, N.J., Gaudi0, K.M., Katz, L.A., Reilly, H.F., Ardito, T.A., Hendler, F.G., and Kashgarian, M. (1984). Beneficial effect of

thyroxin on recovery from toxic acute renal failure. *Kidney Int* 25, 906–911. https://doi.org/10.1038/ki.1984.108

Silva, L.M., Boeing, T., Somensi, L.B., Cury, B.J., Steimbach, V.M.B., Silveria, A.C.O., Niero, R., Filho, V.C., Santin, J.R., and Andrade S.F. (2015): Evidence of gastric ulcer healing activity of Maytenus robusta Reissek: In vitro and invivo studies. *Journal of Ethnopharmacology* 175:75–85

Song, K.I., Kim, S.H., Jang, J.G., and Choi, J.S. (2001). Bromate Intoxication Associated with Acute Renal Failure. *Korean Journal of Nephrology* 732–735.

Sørbye, H., and Svanes, K. (1994). The role of blood flow in gastric mucosal defence, damage and healing. *Dig Dis*. 1994 Sep-Oct;12(5):305-17. doi: 10.1159/000171465. PMID: 7533677.

Sorokin, C. (1973). Dry weight, packed cell volume and optical density. pp. 321–343.

Sterling, K. (2010). Thyroid Hormone Action at the Cell Level. https://doi.org/10.1056/NEJM197901183000304 300, 117–123. https://doi.org/10.1056/NEJM197901183000304

Stuti, M., and D'souza, D. (2013): Effects of Potassium Bromate on the Kidney and Haematological Parameters of Swiss Albino Mice. *The Bioscan* 8(3): 1011-1014

Suzuki, H., Nishizawa, T., Tsugawa, H., Mogami, S., and Hibi T. (2012). Roles of oxidative stress in stomach disorders. *J Clin Biochem Nutr* 50, 35. https://doi.org/10.3164/JCBN.11-115SR

Thá Nassif, A.C., Hintz Greca, F., and Graf, H., Domingues Repka, J.C., Nassif, L.S. (2009). Wound Healing in Colonic Anastomosis in Hypothyroidism. *European Surgical Research* 42, 209–215. https://doi.org/10.1159/000208519

van Lerberghe, W., Keegels, G., Cornelis, G., Ancona, C., Mangelschots, E., and van Balen, H. (1983). Haemoglobin measurement: the reliability of some simple techniques for use in a primary health care setting. *Bull World Health Organ* 61, 957.

Varshney, R., and Kale, R.K. (1990). Effects of calmodulin antagonists on radiation-induced lipid peroxidation in microsomes. *Int J Radiat Biol* 58, 733–743. https://doi.org/10.1080/09553009014552121

Velicky J., Titlbach M., Lojda Z., Duskova J., Vobecky M., Strbak V., and Raska I. (1998): Long-term action of potassium bromide on the rat thyroid gland. *Acta histochem*. 100, 11-23

Venditti, P., and Di Meo, S. (2006). Thyroid hormone-induced oxidative stress. *Cell Mol Life Sci* 63, 414–434. https://doi.org/10.1007/S00018-005-5457-9

Villabona, C., Sahun, M., Roca, M., Mora, J., Gómez, N., Gómez, J.M., Puchal, R., and Soler, J. (1999). Blood Volumes and Renal Function in Overt and Subclinical Primary Hypothyroidism. *Am J Med Sci* 318, 277–280. https://doi.org/10.1016/S0002-9629(15)40631-7

Wada, K., Kamisaki, Y., Kitano, M., Kishimoto, Y., Nakamoto, K., and Itoh, T. (1996). A new gastric ulcer model induced by ischemia-reperfusion in the rat: Role of leukocytes on ulceration in rat stomach. *Life Sci* 59, PL295–PL301. https://doi.org/10.1016/0024-3205(96)00500-0

Waldum, H. L., Sørdal, Ø. F., and Mjønes, P. G. (2019). The Enterochromaffin-like [ECL] Cell—Central in Gastric Physiology and Pathology. *International Journal of Molecular Sciences*, 20(10). https://doi.org/10.3390/ijms20102444

Winzler, R.J. (2006). Determination of Serum Glycoproteins, in: Methods of Biochemical Analysis. John Wiley & Sons, Ltd, pp. 279–311. https://doi.org/10.1002/9780470110188.ch10

Wong, V.W.S., and Singal, A.K. (2019). Emerging medical therapies for non-alcoholic fatty liver disease and for alcoholic hepatitis. Transl *Gastroenterol Hepatol* 4. https://doi.org/10.21037/TGH.2019.06.06

Zhang, G.Y., Langan, E.A., Meier, N.T., Funk, W., Siemers, F., and Paus, R. (2019). Thyroxine (T4) may promote re-epithelialisation and angiogenesis in wounded human skin ex vivo. *PLoS One* 14, e0212659. https://doi.org/10.1371/JOURNAL.PONE.0212659

Zhang, S., and Jiang, J.Q. (2022). Synergistic Effect of Ferrate with Various Water Processing Techniques—A Review. *Water* 2022, Vol. 14, Page 2497 14, 2497. https://doi.org/10.3390/W14162497.