CLINICAL EFFICACY OF URIPRO AMONG PATIENTS WITH HYPERURICEMIA

QENEEL

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MASTER OF PHILOSOPHY
IN
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UNIVERSITY OF VETERINARY AND
ANIMAL SCIENCES, LAHORE
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A THESIS SUBMITTED IN THE PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF

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To,

The Controller of Examination,
University of Veterinary and Animal Sciences,
Lahore.

We, the supervisory committee, certify that the contents and form of the thesis, submitted by Mis Qendeel, have been found satisfactory and recommend that it be processed for the evaluation by External Examiner (s) for the award of the Degree.

Supervisor .....
Dr. Tahir Mehmood Khan

Member .....
Dr. Nabeel Shahid

Member .....
Dr. Adeel Sattar

DEDICATION

Dedicated
To
Holy Prophet Muhammad (Peace Be Upon Him),
My Parents
&
My Supervisor

ACKNOWLEDGEMENTS

I bow my head in utmost gratitude before the most Gracious, the most Merciful and Almighty **ALLAH** without whose will, I could never have accomplished this endearing task, only He gave me the strength and power enough to cope up with all the impediments in the way. I, most modestly, impart my dutiful benefactions to the **Holy Prophet Muhammad** (Peace Be Upon Him) who is persistently a torch of guidance and knowledge for the entire mankind.

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Qendeel

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CHAPTER 1
INTRODUCTION

Gout is a purine metabolism disorder which involves deposition of monosodium urate crystals in peripheral joints and soft tissues when uric acid level rise above the threshold ultimately leading to the inflammation of the specific joints. Hyperuricemia is the underlying cause of gout in which uric acid level in blood rises above 6.8 or 7.0 mg/dl (George and Minter 2020). Uric acid is the product of purine metabolism or cell breakdown which occurs in liver and excreted mostly by kidney. Purine metabolism occur through purine salvage pathway. This pathway works by two ways Firstly, Either it converts adenosine monophosphate to inosine monophosphate in the presence of AMP deaminase which is further converted to inosine by nucleotidase or it converts AMP to adenosine in presence of nucleotidase which is further deaminated to form inosine .Secondly , nucleotidase converts Guanine monophosphate (GMP) to guanosine .Inosine and guanosine are converted to hypoxanthine and guanine respectively in the presence of nucleoside phosphorylase (PNP). Hypoxanthine and guanine which are first converted to xanthine and then to uric acid by the same enzyme xanthine oxidase. So Uric acid is produced endogenously in humans in form of purine metabolite (Maiuolo *et al.* 2016). There is a balance between uric acid production and excretion. Serum uric acid level rises due to decreased excretion or increased production. Precursor of uric acid is either endogenous or exogenous. Endogenous protein precursors are nucleoproteins and exogenous are of dietary origin (meat, sweat bread, liver). Cell breakdown or protein precursors accelerate urate production

Kidneys excrete two third of the uric acid. 90% of uric acid is filtered through glomerular filtration and then it is reabsorbed from S1 segment of proximal tubule through anion transporter (URAT1). Post secretory resorption that is the renal urate excretion phase occurs through ascending loop of henle, distal tubule and collecting duct (de Oliveira and Burini 2012). Decreased renal excretion can occur due to acute renal failure or decreased glomerular filtration. In rare cases deficiency of enzyme due to gene mutation can also increase uric acid level in blood, as in Lesch-Nyhan syndrome HGPRT enzyme (hypoxanthine guanine phosphoribosyl transferase) converts guanine and hypoxanthine into GMP and IMP, respectively is absent. As the enzyme is absent more guanine and hypoxanthine are available to be converted into uric acid (Nanagiri and Shabbir 2020).

Uric acid solubility decreases at lower pH and it starts crystallization. (Loeb 1972) Uric acid starts depositing in joint in the form of monosodium urate crystals after it reaches the saturation point 6.4mg/dl in plasma. Monosodium urate crystals interact with neutrophils (normally present in joints) and attract more neutrophils which triggers inflammation episodes. Furthermore, mast cells interact with MSU secret IL-1ß and activates NLRP3 inflammasome. This leads to inflammation of joints (Chen *et al.* 2017). There are four phases of gout through which it progresses, which are asymptomatic hyperuricemia, chronic tophaceous gout, acute gouty arthritis and intercritical gout. Prolonged asymptomatic hyperuricemia affects a single peripheral joint usually metatarsophalangeal joint which is affected by gout in 56-78% patients. Other joints affected in gout are mid tarsal, ankle, knees, elbows ,wrist and finger (Roddy 2011).Colchicum luteum is a perennial herb with bitter taste small size and dark color. Dried corm of colchicine consists of 0.6% of alkaloid colchicine which amorphous readily soluble in alcohol, water or chloroform. It is used extensively in medicine for gout treatment as It relives inflammation and shorten therapy duration. Colchicine suppresses MSU and activation of NLRP3 inflammasome which suppresses caspase-1 activation involved in IL-1B release and IL18 It has certain side effects like intestinal pain and vomiting (Akhtar 2018), (Slobodnick *et al.* 2018).

Glycyrrhiza glabra (common name mulathi) a perennial shrub is ancient herb with taproot that comprises of glycyrrhizin which is a saponin with anti-inflammatory activity not less than hydrocortisone. Glycyrhizin inhibits phospholipase A2, an enzyme that is involved in inflammation process. Glycyrrhizic acid also inhibits activity of cyclooxygenase and formation of prostaglandin ultimately inhibiting platelet

aggregation which are involved in inflammation process (Kaur *et al.* 2013). Zingiber officinale (ginger) is known for its phytochemicals as It consists of saponins, alkaloids, tannins, flavonoids and glycosides. Major components are gingerol, shagole, gingiberene. Rhizome of Ginger has antioxidant properties on DPPH (α, α-diphenyl-β-picrylhydrazyl), nitric oxide and flavonoid in it has xanthine oxidase inhibition property. Ethanol compound of ginger inhibits xanthine oxidase enzyme similar to that of allopurinol (Muthusamy and Jeyabalan 2019).Lack of adherence to the allopathic treatment of gout occurs due to various side effects associated with them and high cost of therapy. Present study is designed to check the efficacy of a polyherbal formulation in hyperuricemic patients with no side effects. Results will help to find a complementary and alternative treatment therapy which will be cost effective and also it decreases overall burden of disease by resolving the issue of lack of adherence by overcoming the side effects.

CHAPTER 2
REVIEW OF LITERATURE

Gout is an inflammatory disease of joints which is increasing steadily, if left untreated it affects quality of life. Although several allopathic medicines are used for its treatment yet left untreated as lack of adherence occurs because these medicines are associated with many side effects. Therefore, a complementary and alternative treatment with no side effects was required. Many herbal medicines are used for the treatment of gout. Glycerrhiza glabra is one of the herb used in gout as it contains components like Glycyrrhetic acid, liquiritoside, Licochalcone and hydroalcohols which has anti-inflammatory properties (Kaur *et al.* 2013).(Asl and Hosseinzadeh 2008). A study conducted in China in 2008 used BD dose of a herbal formulation modified simiao tang in treatment group and allopurinol 0.1g in control group during a duration of 1month.Modified Simiao tang consist of Cortex Phellodendri 15g, Rhizoma atractylodis 15g, Semen Coicis 30g, Caulis Lonicerae 30g, Radix Achyranthis Bidentatae 15g, Rhizoma Smilacis Glabrae 30g, Radix Paeoniae Rubra 10g, Rhizoma anemarrhenae 15g, Radix Clematidis 15g, Rhizoma Alismatis 10g, Rhizoma Dioscoreae Septemlobae 15g, and Zaocys 15g. CRP and Uric acid were tested and there was a significant decrease in CRP and uric acid in treatment group with herbal formulation as compared to control group (Renbin *et al.* 2008).

Another clinical trial of herbal formulation Shao-Yao Gan-Cao Tang against gout in Taiwan in 2007 was conducted for four weeks. In this trial treatment group was given Shao-Yao Gan-Cao Tang containing Glycyrrhizae Radix and Paeoniae Radix (1:1, w/w) in TDS dose. The serum uric acid levels in the experimental SYGCT group was 0.56 to 0.24 mg/dl at baseline. Hyperuricemic vegetarians with deficient syndrome showed significant improvement in autonomic functions, but the excess-syndrome subjects showed no significant effects (Wu *et al.* 2007).

Colchicum autumnale has been used as antigout from centuries as it relieves pain, inflammation and it also shortens duration of pain (Akhtar 2018). A study was conducted in Pakistan in 2020 for 18weeks which used polyherbal formulation urinile 300mg tablet for 18weeks in treatment group and 300mg allopurinol in control group. Polyherbal formulation i-e urinile tablet consist of equal amount of 500 g of each plant of Apium graveolens seeds, Trachyspermum ammi seeds,Colchicum autumnale tuber, and Berberis vulgeris stem bark. Methanolic extract of these herbs in liquid glucose solution was made and tablets of 300 mg weight were prepared from it. Patients treated with Urinile showed 70% improvement than control group that was treat with allopurinol which showed 67.85% of improvement. (Ahmad *et al.* 2020). A case study of 5 patients in 2020 in India used Unani formulations Habb-e-Suranjan was in use for 30 days. 4 pills three times a day orally (6gm/day) each pills weighing 500 mg.Habb-e-Suranjan consist of Sibr Saqootri (Aloe barbadensis), Post Halela Zard (Terminalia chebula), Suranjan Sheerin (Colchicum autumnale) All the drugs were taken in equal weight. Patients signs and symptoms of gout were improved by given Unani formulation and no adverse effect of Unani formulation was noted in the patient (Parveen *et al.*).A study in Taiwan for 1month used Danggui-Nian-tong tang 500mg herb powder filled in capsule 6 capsule per day in TDS. Danggui-Nian-tong tang consist of Notopteryium incisum Ting 5gm, Artemisia capillaris Thunb 5gm, Scutellaria baicalensis Georgi 5gm, Glycyrrhiza unbellatus (Per.) 3gm, Alisma orientalis (Sam.) Juzep 3gm, Saposhnikovia divaricate (turcs.) schischk 3gm, Angelicasinensis (Oliv.) Diels. 2gm, Atractylodes lancea (Thunb.) DC. 2gm, Pueraria lobata (Wild.) Ohwi. 2gm, Panax ginseng C.A.Mey. 2gm, Sophora flavescens Ait. 2gm, Cimicifuga heracleifolia Kom. 2gm, Atractylodes macrocephala Koidz 1.5gm (Chou and Kuo 1995).

In China a study was conducted for 2-week period in which experimental group was given oral 600 mL decoction of Simiao Pill in 3 portions once daily. Simiao pill contains Rhizoma Atractylodis 20g, Semen Coicis 30g Cortex Phellodendri 20g, Rhizoma Smilacis Glabrae 30g, Radix Cyathulae 30 g, Caulis Lonicerae20g, Radix Paeoniae rubra 20g, Rhizoma anemarrhenae 20g, Gypsum Fibrosum 50 g, and Ramulus

Cinnamomi 5g. Indomethacin was given to control group at 50 mg 3 times a day. When the symptoms improved, the dose was reduced to 25 mg, 3 to 4 times a day. The efficacy of herbal product was 96% as compared to indomethacin which was 68% (Shi *et al.* 2008). Herbal formulation was used in China in 34 patients during a clinical trial for 1week.Experimental group was treated with bloodletting cupping alongwith 500ml herbal decoction. Herbal medicine contain Caulis lonicerae 15g, Herba speranskiae 15g, Rhizoma Smilacis Glabrae 10g, Radix Cynanchi Paniculati 15g, Semen Coicis 20g, Cortex phellodendri 10g, Fructus Gardeniae 15g, Herba Plantagini 15g, Rhizoma Dioscoreae Septmlobae 15g and Talcum 20g .For 20 minutes these herbs were soaked in 800ml of water and decocted till boiling on strong fire and then with slow fire for 20 minutes. 25 mg of enteric coated Diclofenac Sodium tablets were given to control group for three times daily for 3–7days. The index of joint swelling was 0, and the serum uric acid reduced to normal. Cure rate in treament group was 61% and 58% in control group (Zhang *et al.* 2010).

In a multicenter controlled randomized study in China Polyherbal fomulation COTOL was used. It contains Rhizoma smilacis Glabrae 30g, Stigma maydis 15g, Rhizoma dioscoreae collettii 30g, Curcuma longa 12g, and Rhizoma corydalis 18g, Semen coicis 30g, Loranthus parasiticus15g, and Herba siegesbeckiae 18g. The patients with control group were treated with a placebo consists of 20g of charred millet sprout, edible bitter principle 3g, charred fructus crataegi 12g, and fructus hordei germinates 20g each have no therapeutic effects on gout. CoTOL reduced serum uric acid levels and prevented recurrence of acute arthritis in chronic and intercritical gout with no serious adverse event (Xie *et al.* 2017). Zingiber officinale is a herb with anti-inflammatory properties. An *in-vitro* study was carried out which measured the activity of the enzyme xanthine oxidase using UV spectrophotometry. Zingiber extract was prepared by cold maceration and shade drying of the herb. Phytochemical study showed that Flavonoid present in it reduces blood uric acid through inhibiting the xanthine oxidase. *in-silico* docking studies also suggest that most of the phytoconstituents of Zingiber officinale rhizome passes the drug likeness properties as such standard drug allopurinol (Muthusamy and Jeyabalan 2019). An open label single arm study was carried out in India for 3month.In this study patient was given 1 tablet of CV-HFG01 (herbal formulation) twice daily orally with water for 3 months along with the ongoing treatment.CV-HFG01 comprises of Shodhit guggul/ Commiphora mukul, Harad / Terminalia chebula, Behada/ Terminalia bellirica, Awala /Emblica officinalis, Guduchi / Tinospora cordifolia, Sounth/ Zingiber officinale, Piper nigrum, Piper longum, Operculina turpethum, Vayavidanga / Embelia ribes,Anantmool/ Hemidesmus indicus. Treatment of CV-HFG01 demonstrated significant reduction in uric acid levels, pain, and stiffness in patients suffering from gout (Deo *et al.* 2019).

Wathania somnifera is herb with many bioactive compounds like withaferin A , withanolide D. beta-sisterol, Anaferine, anahygrine, chlorogenic acid.(Akram *et al.* 2011). An invitro study showed that it contains several alkaloids, withanolides, reducing sugars and flavonoids. The effect of *W. somnifera* was checked on inflammation in rats that was induced by monosodium urate crystals. The powder of roots of Wathania somnifera root decreased the release of enzyme from PMNL cells that was induced by the monosodium urate crystals which suggested that it could save tissues from harmful effect of these enzymes thus reducing inflammatory response. Rats treated with the root powder of Wathania somnifera did not show any ulcerogenic effect in stomach fasting of 16hrs, whereas rats treated with indomethacin produced small erosions throughout stomach (Rasool and Varalakshmi 2006).

Piper longum commonly known as long pepper is known for its bioactive components and its use as spice.It contains volatile oil, protein, alkaloids and saponins. Major alkaloids are Piperine, piperlonguminine, Piperlongumine and trimetoxycinnamate. Piperine inhibits COX-1 and lipoxygenase, thus providing analgesic and anti-inflammatory effect.Moreover it is anti-asthmatic, immunomodulatory and hepatoprotective. These properties are adding to the effect of Uripro (Khushbu *et al.* 2011). Boerhavia diffusa commonly known as punarnava consit of many phytochemicals isoflavonoids, flavonoids, *xa*nthones, purine nucleoside, lignans, and steroids. Methanol extract in it have antioxidant, cytotoxic activity ,anti-inflammatory and thrombolytic(Mishra *et al.* 2014). activity.

Glycyrrhiza glabra (common name mulhatti) a perennial shrub is ancient herb with taproot that comprises of glycyrrhizin which is a saponin with antiinflamatory acivity not less than hydrocortisone. Glycyrhizin inhibits phospholipase A2, an enzyme that is involved in inflammation process. Glycyrrhizic acid also inhibits activity of cyclooxygenase and formation of prostaglandin ultimately inhibiting platelet aggregation which are involved in inflammation process (Kaur *et al.* 2013). This inflammation reduction property must be adding to the symptomatic treatment of gout.

Zingiber officinale (ginger) is known for its phytochemicals as It consists of saponins, alkaloids, tannins, flavonoids and glycosides. Major components are gingerol, shagole, gingiberene. Rhizome of Ginger has antioxidant properties on DPPH (α, α-diphenyl-β-picrylhydrazyl), nitric oxide and flavonoid in it has xanthine oxidase inhibition property. Ethanol compound of ginger inhibits xanthine oxidase enzyme similar to that of allopurinol (Muthusamy and Jeyabalan 2019).This xanthine oxidase inhibition property could be decreasing uric acid level.

The decoction used for enema consisted of crude rhubarb 30 g, calcined oyster shell 50 g, waterplantain rhizome 30 g, red sage root 15 g, sophora flower 30 g, aconite root 15 g, and scullcap root 30 g. It was boiled down to 500 mL of decoction. In enema, 150 mL of the decoction was used each time for high enema (20-30 cm) and reserved there for over 60 min. treated group, significant improvements were shown in terms of blood levels of triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), as well as 24 h U-mAlb, pH in urine, and 24 h amount of urine. Levels of SUA, BUN and SCr, as well as CCr were significantly improved after treatment in the treated group but in the control group, these indices, except SUA were improved insignificantly (Chen *et al.* 2009)

It consists of Chlorogenic acid: 205.6 μg/ml 2: Loganin: 36.2 μg/ml 3: Resveratrol: 149.2 μg/ml. Chuanhu anti-gout mixture given 250 ml orally daily. Chuanhu anti-gout mixture was non-inferior to Colchicine in lowering the recurrence rate (treatment difference within the prespecified non-inferiority margin of 15%), white blood cell count (treatment difference within the prespecified non-inferiority margin of -0.5×109/L), and C-reactive protein (treatment difference within the prespecified non-inferiority margin of -1.0 mg/L). The Chuanhu anti-gout mixture was associated with a better effect in relieving pain in the affected joint, but it was not associated with changes of swelling and limitation scores of the affected joint, or with blood urea nitrogen, blood sugar, triglycerides and total cholesterol, compared to Colchicine. Chuanhu anti-gout mixture was associated with significantly fewer adverse events (especially diarrhea) and lower levels of aspartate aminotransferase, alanine aminotransferase, creatinine and blood uric acid compared to Colchicine (Wang *et al.* 2014).

It consist of Rhizoma smilacis Glabrae (Smilax glabra, Tufuling) 30g, Rhizoma dioscoreae collettii (Dioscoreatokoro Makino, Bixie) 30g, Curcuma longa (turmeric 12g, Jianghuang), Herba siegesbeckiae 18g(Glandularstalk St.Paul's Wort herb, Xixiancao), and Rhizoma corydalis 18g(Yanhusuo, Yanhusuo), Semen coicis 30g (coix seed, Yiyiren), Loranthus parasiticus15g (Chinese taxillus twig, Sangjisheng), and Stigma maydis 15g (corn silk, Yumixu). CoTOL given 2 packs a day (Xie *et al.* 2017).

It contains Earthworm 10g, Cardamon 6g, Cortex Phellodendri 10g, Atractylodes 9g, coix seeds 20g, cyathula 10g. receive either YWF decoction, YWF + gypsum 15g decoction, orally three times daily (100 mL each time) for four weeks. YWF decreased uric acid.but there is no difference in uric acid upon adding gypsum (Yu *et al.* 2018)

Statement of problem

Hyperuricemia is a prevailing condition in Pakistan which advances into gout. It is risk factor to many renal and cardiovascular diseases and medication adherence is very low. Allopathic medicine has

many side-effects which can be the major cause of lack of adherence to its treatment. The study has following objectives.

- To conduct an interventional study to explore the effect of URIPRO among Hyperuremic and Symptomatic patients.
- To Conduct a Cost analysis of Anti-Uremic Advance and Complementary Medicines.
- To explore the factors affecting the adherence of patients with Uremic therapy.
- To conduct a systematic review and Meta-analysis to rule out the comparative efficacy of herbs vs standard treatment of hyperuricemia.

CHAPTER 3
MATERIALS AND METHODS

3.1 Effect of URIPRO among Hyperuricemic and Symptomatic patients.

3.1.1 Aims:

The aim of study is to evaluate the efficacy and safety of test product 'Uripro tablets' for the treatment for hyperuricemia, gout and symptoms associated with them

3.1.2 Design and setting of study:

This was an open label quasi, single arm, longitudinal, interventional clinical study in patients with hyperuricemia and gout. Patients were informed about the study and written informed consent was obtained from the participants. This study was conducted at Health care center at Lahore City, Pakistan.

3.1.3 Patients:

31 out-patients of hyperuricemia who visited the clinic, aged 31-73 with average 51years were included in this study. 13 patients were with age below 50 while 12 were above 50 years.

3.1.4 Diagnostic criteria:

Patients were classified as gout patient according to the set criteria by collaborative initiative of ACR (American college of Rheumatology) and European League Against Rheumatism (EULAR) in 2015 which involves 1) Pattern of joint involved, 2) Characteristics of symptomatic episode, 3) Time duration of symptomatic episode, 4) Evidence of tophus, 5) Level of Serum urate 6) Analysis of Synovial fluid, 7) Imaging of evident of urate deposition, 8) Imaging of joint damage due to gout. Those patients with score equal to 8 or above are diagnosed with gout. According to NHANES III laboratory definition female with uric acid >5.7mg/dl and male with uric acid >7mg/dl were classified into hyperuricemia.

3.1.5 Inclusion criteria:

Adults with 18 years age or older having a diagnosis of gout according to ACR/EULAR or confirmed hyperuricemia as per NHANES III definition and those who agreed to participate in study through informed consent were eligible to participate in the study.

3.1.6 Exclusion criteria:

Patients who participated in any other clinical trial in past 3 months were not included in the study. Participants that do not follow inclusion criteria, Pregnant, lactating or breast-feeding females, patients with severe liver, heart or kidney disease, mental illness, were also excluded from the study.

3.1.7 Falling off standard:

Criteria for the discontinuation of the study was follows1) Patients with lost follow-up, 2) having severe ADRs 3) withdrawal of consent.

3.1.8 Sample size:

As this was a pilot study So, 31 participants were included in this study.

3.1.9 Medicine:

Uripro a polyherbal Formulation was provided by Awami Laboratories. The main ingredients were Piper nigrum, Zingiber officinale, Colchicum luteum, Withania somnifera, Glycyrrhiza glabra, Boerhavia diffusa, Piper longum etc. as shown in table 3.1.

Table 3.1 Composition of URIPRO

Ingredient	Common Name	Strength
Piper nigrum	Black Pepper	91mgS
Zingiber officinale	Ginger	130mg
Colchicum luteum	Suranjan	130mg
Withania somnifera	Withania	104mg
Glycyrrhiza glabra	Licorice	65mg
Boerhavia diffusa	Punarvana	39mg
Piper longum	Pipali	39mg

3.1.10 Intervention (Dosage and treatment duration):

Participants were given a dose of Uripro 2 tablets two times a day for 4 weeks. Age, height, body weight, gender, and the presence of hypertension, CVS, diabetes, GIT disorders, cerebrovascular disease, kidney disease, dyslipidaemia and smoking status was noted in all participants. Participants were advised to make lifestyle modifications like walk, normal rest, low purine diet, drinking water >2L/day. Participants were called for follow-up at day 20 and 30.

3.1.11 Items for observation:

Primary outcome of observation was serum uric acid concentration (mg/dl) which was determined by commercially available diagnostic kit.

Secondary outcome was change in clinical symptoms associated with gout like pain, redness/swelling, and restoration of Lab parameters i.e ESR, renal function indices serum creatinine, blood urea, Liver function test indices ALT, AST,total bilirubin, Gamma GT, Alkaline phosphatase and CBC parameters Haemoglobin ,Leucocyte count, platelets to normal.

3.1.12 Criteria for Evaluation:

Serum uric acid was evaluated by mean percentage decrease in serum uric acid from the baseline. Pain score was assessed by Budzynski index of pain. Criteria of this scale is as follows 0)for no pain 1)pain which can be tolerated, 2) pain which can't be tolerated but do not effect daily work, 3) pain that cannot be

ignored and involve mind disturbance, 4) pain that effect daily work 5) pain that leads to work absence and patient had to take a bed rest. Swelling was assessed by the following criteria 0) no swelling,1) mild selling, 2) moderate swelling, 3) severe swelling. Lab parameters were assessed by a lab, mean difference in the lab values before and after the treatment was noted.

3.1.13 Statistical analysis:

The data was analysed by using MS-Excel and SPSS version 20.0 software for the appropriate non-parametric statistics such as mean, median and standard deviation. Paired t-test was used for the comparison between before and after the treatment therapy. The level of significance was 0.05 with 95% confidence interval.

3.2 Cost analysis of Anti-Uremic Advance and Complementary Medicines.

An observational study was conducted at institute of pharmaceutical sciences Lahore between the month of October 2020 and February 2021. The cost of registered brands of a particular drug with one active pharmaceutical ingredient, same strength and dosage manufactured by different pharmaceutical companies was compared. Pharma guide was utilized to infer the cost of anti-gout drugs registered in Pakistan. Pharma guide is a medical reference handbook that contains the authentic information regarding pricing and brands available in the specific country. Pharma guide contains the consumer price of available brands in pack size. Anti-gout medicine with same strength and single API (Active pharmaceutical ingredient) that are registered in solid dosage form and manufactured by two or more than two different pharmaceutical companies were analysed in this study. Combination medicines were not included in the study. Data regarding registered brands, their number, formulation and number of manufacturing companies were collected. Data regarding cost of all anti-gout drugs with multiple strengths available in different brands and manufactured by various pharmaceutical companies was collected on Microsoft excel spreadsheet. As pharma guide provide the price of pack of the medicine so, for comparison of their prices tablet's unit cost was derived. For each formulation difference of highest and the lowest price was noted, and percentage price variation was calculated. Anti-gout drugs were sub categorized into different classes such as uricostatic, uricosuric, NSAIDS, immunosuppressive and corticosteroids.

3.2.1 Statistical analysis

All brands of anti-gout drugs consisting of various salts available in Pakistan were noted and single unit price of these brands was calculated. Then on basis of registered brands percentage contribution of each class of anti-gout drugs among total brands was calculated. Maximum and minimum prices of brands available for each drug was noted in Microsoft excel spreadsheet. Then price difference of these anti-gout drugs was calculated by finding difference in highest and lowest price brand. Then price variation was derived by following formula:

$$\text{Price Variation} = \frac{\text{price of most costly brand} - \text{price of most economic brand}}{\text{price of most economic brand}} \times 100$$

3.3 A Systematic Review on traditionally used herbs against hyperuricemia and gout

A systematic review was carried out to find research papers out of 4 data bases from the 2000 till date 4th January 2021. The Systematic review was performed, according to recommendations of PRISMA (Preferred reporting items for systemic review and meta-analysis), to rule out the comparative efficacy of herbs vs standard treatment of hyperuricemia.

3.3.2 Population intervention comparator and outcomes

Respective population: Patient with gout or hyperuricemia.

Intervention: Herbal formulation or alternative therapy.

Comparator: Placebo or any Allopathic treatment.

Outcomes: Change in uric acid and symptoms of gout.

3.3.3 Search strategies

Four electronic databases which includes Cochrane, Pubmed, Science direct and google scholar were searched using following search terms herbal treatment OR Chinese herbs OR Asian herbs OR north Americans herbs OR herbs OR traditional herbs OR hyperuricemia OR gout.

All papers searched were imported to endnote file and a library was created. All duplicates were searched and removed. Firstly, titles were screened and then abstracts were studied. Full text was downloaded and studied for inclusion criteria on the basis of set criteria of exclusion and inclusion as described below. Figure shows an overview of studies included.

3.3.4 Study Selection:

The following is the criteria for the inclusion and exclusion of the studies to find out potential papers for our interest.

3.3.4.1 Inclusion Criteria.

- All studies with English language were considered eligible.
- All studies from January 1st, 2000 to January 31st, 2021 were included.
- Only human clinical trials using any herbs for gout and hyperuricemia treatment were included.
- Outcome which included change in serum uric acid and gout symptoms was included.

3.3.4.2 Exclusion Criteria.

- All studies with language other than English were excluded.
- Experimental Animal studies were excluded.
- Systematic review, case repots, Opinions, unpublished thesis or reports, letters to editor were not included.

3.3.4.3 Outcome of interest.

- Primary outcome: Change in uric acid and symptoms of gout specially pain.
- Secondary Outcome: inflammation, tolerability and safety of treatment applied.

3.3.5 Data Extraction:

Data regarding the following aspects was extracted in a systematic way and entered in Microsoft excel sheet. Initially for parameter's template two studies were selected. Later more remaining studies were added to the already existing templates. Following parameters were extracted.

- Study characteristics (Study title, First author, Year and country of publication, study design, Study period).
- Patient's characteristics (Sample size, gender, age and ethnicity).
- Intervention (herbal treatment dose and total time of therapy).
- Comparators (type, dose, and length of therapy).
- Outcomes that include change in uric acid and symptoms of gout after intervention group and control group consumed therapy.
- Data obtained was presented in tabulated form.

3.3.6 Risk of bias (Quality) Assessment

Quality of randomized controlled trials included in the study was checked by using risk of bias (ROB). For this purpose, Cochrane risk of bias tool was used. This tool consists of six domains of study for the assessment of ROB which are as follows:

- Random Sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective reporting
- Other bias

All these domains are labelled as 'high risk' if the risk of biasness is high, 'low risk' if the risk of biasness is unlikely to effect and 'unclear risk' if risk of biasness is unclear. Conflict in determination was assessed by conversation with the Supervisor.

3.4 factors affecting the adherence of patients with Uremic therapy

3.4.1 Research setting and data:

Data was collected from community setups in Lahore, Pakistan over the period of 6 months from July 2021. Data regarding demographics including age, height, weight, BMI, education level, disease history, current medication and adherence was collected.

3.4.2 Study population and design:

Patients who were aged 18 years or above and dispensed with gout or hyperuricemia medicine between 1st February 2021 to 31 July 2021 were enrolled in the study during this 6-month period.

3.4.3 Adherence measure:

Questionnaire using 6 parameters was used for this study. It was based on patient reporting face to face and used for evaluation of drug adherence. It was 6 item questionnaires with scores ranging 0 to 6. Criteria was set as Higher the score lower will be the adherence rate. Zero score was classified as high adherence,0-2 as moderate adherence and 3-6 as low adherence rate.

3.4.4 Covariates and measure:

Patient characteristics were analyzed and correlated to different factors for adherence. These factors include age, sex, comorbid conditions. Current medication of patients regarding hyperuricemia and gout which

include xanthine oxidase inhibitors, anti-inflammatory, colchicine and uricostatic were identified. Patients taking urate lowering agents prophylactically were also identified.

3.4.5 Statistical analysis:

Statistical analysis was performed using SPSS. Descriptive frequency analysis was performed on demographics. Regression analysis was carried out to check association with patient characteristic, comorbidities and adherence score with a confidence interval of 95%.

CHAPTER 4
RESULTS

4.1 Interventional study to explore the effect of URIPRO among Hyperuricemia and Symptomatic patients:

The results for the Interventional study to explore the effect of URIPRO among Hyperuricemia and Symptomatic patients are as follows.

4.1.1 Participants flow

A total 31 participants were enrolled in the study and six dropped out during study as shown in figure 4.1.

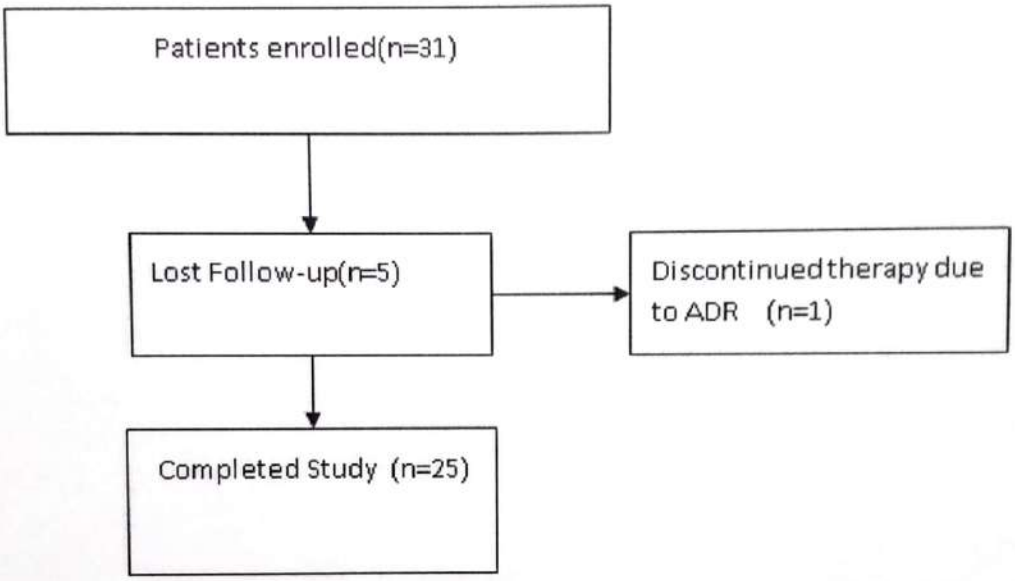

Figure 4.1 Flow chart for patient's enrolment for the study

4.1.2 Baseline characters:

25 participants who continued the study were with the mean age 51±10 years (range 31-73), predominantly female 76% while male were 24%. The mean BMI(body mass index) was 30±6kg/m^2(22-46).36% patients were with cardiovascular disease and 56% were with GIT disorder.12% patients had smoking status.60% patients were with hypertension and 4% with kidney disease. Details of demographics are shown in table 4.1. All the patients were hyperuricemic as per classification of NHANES III set criteria while 2 were with gout as per classification of ACR and EULAR.

Table 4.1 Demographics and comorbidities of 25 patients for the study

Age(years)	51±10(31-73)
≤50	13
>50	12
Height(cm)	162±6(151-176)
Weight(kg)	78.92±17(51-110)
BMI (kg/m²)	30±6(22-46)
Gender	
Male (%)	6(24%)
Female (%)	19(76%)
Occupation	
Govt. Employ	1(4%)
Housewife	19(76%)
Entrepreneur	3(12%)
Unemployed	1(4%)
Driver	1(4%)
Cardiovascular Disease	9(36%)
Cerebrovascular Disease	4(16%)
Kidney Disease	1(4%)
Hypertension	15(60%)
Dyslipidemia	6(24%)
GI Disorder	14(56%)
Smoke	3(12%)

BMI is Body Mass Index expressed in kg/m²

4.1.3 Primary Outcome:

4.1.3.1 Serum uric acid:

Serum uric acid significantly decreased after the treatment. Mean serum uric acid (SUA) difference at 1st follow-up was 0.8±1.2 ranging from 0.3-1.3mg/dl which further decreased at 2nd follow up with mean SUA difference of 1.3 ±0.9 ranging from 0.75-1.9mg/dl with $p<0.05$. Table 4.2 summaries the mean serum uric acid difference with $p<0.05$.

Table 4.2 Uric acid level comparison (before and after treatment)

Parameter	Paired Differences				t	Sig. (2-tailed)
	Mean difference	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Uric Acid at base level - Uric Acid at 1st Follow-up	0.808	1.2083	0.3092	1.3068	3.344	0.003
Uric Acid at base level - Uric Acid at 2nd Follow-up	1.3417	0.9239	0.7547	1.9287	5.031	0

4.1.4 Secondary Outcome:

4.1.4.1 Clinical symptoms:

Baseline parameters of the participants include joint stiffness in 88% patients while 56% participants were experiencing episodes of pain and one with evidence of tophus. 28% participants have mis-happened joints. 32% patients involve MTP1 joint 52% with ankle/midfoot and 88% involve other joints which is summarized in table 4.3.

Table 4.3 Other parameters at baseline

Joint stifness	22(88%)
Evidence of tophus	1(4%)
Previous episodes of pain	14(56%)
Joints involved	
MTP1	8(32%)
Ankle/Mid Foot	13(52%)
Other Joint	22(88%)
Mishappen joint	7(28%)
Urinary stone	0(0%)
Gout	2(8%)

4.1.4.2 Pain score:

Pain score decreased significantly ($p<0.05$) after treatment with an effective rate of 96%. At baseline 1 case was with score 0, 4 cases with score 2, 13 cases with score 3, 7 cases with score 5 totalling 82 score before treatment and at 1st follow up 18 cases score 0,5 cases score was 2 and 2 cases score was 3 with total score of 16 and at 2nd follow up only one case was with score 2 while all other were with score 0 as shown in table 4.4. Mean pain score difference between the enrolment and 1st follow-up was 2±1.5 (2-3) with $P<0.05$ while it was 3±1.3 with $P<0.05$ as shown in table 4.5.

Table 4.4 Pain Score of the Patients

Pain Score	At enrollment	1st Follow-up	2nd Follow-up
0	1	18	24
1			
2	4	5	1
3	13	2	
4			
5	7		

Table 4.5 Mean Pain Score Difference

Parameter	Paired Differences				t	Sig. (2-tailed)
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Joint Pain at Enrollment - Joint Pain at 1st Followup	2.6400	1.5242	2.0108	3.2692	8.660	.000
Joint Pain at Enrollment - Joint Pain at 2nd Followup	3.2857	1.3801	2.0093	4.5621	6.299	.001

4.1.4.3 Swelling Score:

Comparison between the pre-treatment and post-treatment showed that the swelling score has been significantly decreased with a total effective rate of 91% and 95% decrease in difficulty of joint movement as

described in table 4.7 while mean swelling score difference at 1st follow up was 1.2±0.9 and at 2nd follow up it was 1.5±1.3 with $p<0.05$ as shown in table 4.6.

Table 4.6 Mean Swelling Score Difference

Parameter	Paired Differences				t	Sig. (2-tailed)
	Mean	Std. Deviation	95% Confidence Interval of the Difference			
			Lower	Upper		
Redness and Swelling at Enrollment - Redness and Swelling at 1st Follow-up	1.2000	.8944	.7814	1.6186	6.000	.000
Redness and Swelling at Enrollment - Redness and Swelling at 2nd Follow-up	1.5000	1.3093	.4054	2.5946	3.240	.014

4.1.4.4 Indigestion: 32% patients at enrolment has indigestion issue and total effective rate was up to 75% at the second follow-up as shown in table 4.7.

Table 4.7 Comparison of symptoms before and after treatment

Time	Arthralgia	Joint inflammation	Limited Joint Activity	Indigestion	Can't bear pressure
At enrollment	24(96%)	21(84%)	20(80%)	8(32%)	5(20%)
At 1st Followup (% resolution)	17(68%)	14(56%)	15(60%)	3(12%)	5(20%)
At 2nd Followup (% resolution)	6(24%)	5(20%)	4(16%)	3(12%)	–
Total Effective Rate	23(96%)	19(91%)	19(95%)	6(75%)	5(100%)

4.1.4.5 Lab parameters:

The levels of uric acid, AST, ALT decreased significantly ($p<0.05$) after treatment while other parameters have non-significant differences as shown in table 4.8.

4.1.4.5.1 RFT:

Among other RFT parameters Blood urea decreased non significantly after the treatment with a mean difference of 1.04± 9 mg/dl (P>0.05) while serum creatinine did not change as the mean difference was zero before and after the treatment.

4.1.4.5.2 LFT:

Among LFT parameters AST and ALT decreased significantly with mean difference of 2.24±5U/L, 5.36±7.7U/L (P<0.05) respectively while the other parameters Gamma GT, Total Bilirubin and Alkaline Phosphatase decreased non-significantly (P>0.05).

4.1.4.5.3 CBC:

Among CBC parameters White blood cells decreased with a mean difference of 0.46($\times 10^9$/L) ±3.8, Platelets decreased with a mean difference of 5.32($\times 10^9$/L) ± 49 while Hemoglobin increased with a mean difference of 0.09±0.34g/dl. ESR decreased with a mean difference of 0.84±7.7mm/1st Hour.

Table 4.8 Comparison of Lab Parameters (Mean Difference between value pre and post treatment)

	Paired Differences				t	p value (Sig. (2-tailed)
Parameters	**Mean Difference**	**Std. Deviation**	**95% Confidence Interval of the Difference**			
			Lower	**Upper**		
Blood Urea at Enrollment - Blood Urea at 1st Followup	1.04	9.85	-3.03	5.11	0.53	0.60
Serum Creatinine at Enrollment - Serum Creatinine at 1st Followup	-0.03	0.18	-0.11	0.04	-0.96	0.35
ALT at Enrollment - ALT at 1st Followup	5.36	7.75	2.16	8.56	3.46	0.00
AST at Enrollment - AST at 1st Followup	2.24	5.35	0.03	4.45	2.09	0.05
Gamma GT at Enrollment - Gamma GT at 1st Followup	4.00	29.59	-8.50	16.50	0.66	0.51
Total Bilirubin at Enrollment - Total Bilirubin at 1st Followup	0.34	1.41	-0.24	0.92	1.20	0.24
Alkaline Phosphate at Enrollment - Alkaline Phosphate at 1st Followup	9.20	42.37	-8.29	26.69	1.09	0.29
WBC at Enrollment - WBC at 1stFollowup	0.46	3.84	-1.12	2.05	0.60	0.55

Hb at Enrollment - Hb at 1st Followup	-0.09	0.61	-0.34	0.16	-0.76	0.46
MCV at Enrollment - MCV at 1st Followup	-0.24	1.47	-0.85	0.37	-0.82	0.42
MCH at Enrollment - MCH at 1stFollowup	-0.24	0.85	-0.60	0.11	-1.43	0.17
Platelets at Enrollment - Platelets at 1stFollowup	5.32	49.30	-15.03	25.67	0.54	0.59
RBC at Enrollment - RBC at 1stFollowup	0.03	0.23	-0.07	0.12	0.55	0.59
Lymphocytes at Enrollment - Lymphocytes at 1st Followup	1.43	8.24	-1.97	4.83	0.87	0.39
Monocytes at Enrollment - Monocytes at 1st Followup	-0.03	2.29	-0.98	0.92	-0.06	0.95
Eosinophils at Enrollment - Eosinophils at 1st Followup	0.36	1.49	-0.26	0.97	1.19	0.25
ESR at Enrollment - ESR at 1st Followup	0.84	7.74	-2.35	4.03	0.54	0.59

4.2 Cost analysis of Anti-Uremic Advance and Complementary Medicines:

The results for the Cost analysis of Anti-Uremic Advance and Complementary Medicines are as follows:

According to this study 13 registered salts with 31 different strengths in mg make 1307 brands of four different classes of anti-gouts as shown in table 4.9.

Table 4.9 Contribution of antigout in total registered brands

Drug Class	No. of molecule in each class	Total Brands of all strength	Percentage in total
Uricostatic	2	49	3.75
antiInflamatory drugs	2	12	0.92
NSAIDS	8	1245	95.26
Uricosuric agents	1	1	0.08
Total	13	1307	

331 different manufacturing companies are involved in the manufacturing of all these 1307 brands. Among the all registered brands Non-steroidal anti-inflammatory drugs lead with 95.26% (1245/1307), uricostatic are second contributor with 3.75% (49/1307) and other anti-inflammatory drugs are the third on the list which make up to 0.92% (12/1307). Diclofenac 50mg makes up the first largest salt among the total brands registered in Pakistan with a proportion of 19.36% (253/1307) while mafenamic acid 250mg is the second contributor with a proportion of 12.7% (167/1307).Table 4.10 represents anti-gout drugs percentage contribution among their respective class and within all brands registered in Pakistan.

Table 4.10 Contribution of registered brands in different classes and individual antigout

Anti-gout	No. of Brands	Strength(mg)	Contribution within class	Contribution within brands
Uricostatic	49			
Febuxostat	23	40	46.94	1.76
Febuxostat	18	80	36.73	1.38
Febuxostat	1	120	2.04	0.08
Allopurinol	2	100	4.08	0.15
Allopurinol	5	300	10.20	0.38
Anti-inflamatory drugs	12			
Colchicine	1	0.5	8.33	0.08
Prednisolone	11	5	91.67	0.84
NSAIDS	1245			
Aspirin	21	75	0.02	1.61
Aspirin	1	100	0.00	0.08
Aspirin	12	150	0.01	0.92
Aspirin	56	300	0.04	4.28
Aspirin	1	500	0.00	0.08
Celecoxib	36	100	0.03	2.75
Celecoxib	49	200	0.04	3.75
Diclofenac	19	25	0.02	1.45
Diclofenac	253	50	0.20	19.36
Diclofenac	61	75	0.05	4.67
Diclofenac	37	100	0.03	2.83
Etoricoxib	4	60	0.00	0.31
Ibuprofen	99	200	0.08	7.57

Ibuprofen	117	400	0.09	8.95
Ibuprofen	13	600	0.01	0.99
Mefnamic acid	167	250	0.13	12.78
Mefnamic acid	73	500	0.06	5.59
Naproxen	1	50	0.00	0.08
Naproxen	60	250	0.05	4.59
Naproxen	14	275	0.01	1.07
Naproxen	98	500	0.08	7.50
Naproxen	36	550	0.03	2.75
Naproxen	2	750	0.00	0.15
Indomethacin	15	25	0.01	1.15
Uricosuric agents	1			
Probenecid	1	500	1.00	0.08
Pegloticase	0		0.00	0.00
	1307			

As far as price variation is concerned among uricostatic drugs febuxostat 40mg showed highest price variation of 89% (per tablet price in PKR ranges from 9.5 to 18), allopurinol showed percentage price variation up to 33% , that is 32% (per tablet price ranges from PKR 1.2 to PKR 1.6).In uricostatic group febuxostat 120mg showed the least price variation (0%). Among NSAIDs ibuprofen 400mg showed the highest percentage price variation among its brands that was 14400% (per tablet price ranging from PKR 0.1 to PKR 14.5), it was the highest price variation among the all brands available for gout and hyperuricemia treatment. Among other anti-inflammatory drugs class prednisolone showed the highest price variation in percentage that was 1400% (per tablet price ranges from PKR 0.2 to PKR 3) and, while Colchicine showed no price variation as it is available in only in single brand. Table 4.11 represents the percentage price variation of all drugs available for hyperuricemia and gout treatment. Among all the available brands febuxostat 120mg, colchicine, aspirin 500mg and 100mg and naproxen 50mg showed no price variation.

Table 4.11 Percentage price variation among different brands

Drug	Formulation	Dose (mg)	No. of manufacturing companies	Max price per tablet	Min price per tablet	Percentage variation
Uricostatic						
Febuxostat	3	40	23	18	9.5	89
		80	18	33	19.4	70
		120	1	40	40	0
Allopurinol	2	100	2	1.6	1.2	33
		300	5	4.63	3.5	32
Anti-inflammatory drugs						
Colchicine	1	0.5	1	3.2	3.2	0
Prednisolone	1	5	11	3	0.2	1400
NSAIDS						
Indomethacin	1	25	12	2.75	0.2	1275
Aspirin	5	75	21	1.1	0.1	1000
		100	1	0.8	0.8	0
		150	12	1.5	0.8	88
		300	41	2.1	0.1	2000
		500	1	1.1	1.1	0
Celecoxib	2	100	33	23	2.5	820
		200	42	20	4.8	317
Diclofenac	4	25	17	3.6	0.4	800
		50	188	10	0.3	3233
		75	43	12	2.9	314
		100	32	10	3.5	186

Etoricoxib	1	60	4	10	10	0
Ibuprofen	3	200	64	43	0.3	14233
		400	84	14.5	0.1	14400
		600	12	14.2	0.8	1675
Mefnamic acid	2	250	92	8.8	0.1	8700
		500	60	2.2	0.4	450
Naproxen	6	50	1	3.5	3.5	0
		250	56	8.8	2.8	214
		275	14	6.3	3.5	80
		500	87	14.3	3.5	309
		550	34	71.6	4.2	1605
		750	2	22.8	10	128

Whisker box plot is plotted for different classes of medicines (Selective NSAIDs, non-selective NSAIDs and others including uricostatic drugs) separately to graphically compare the prices of different generics. Among the Uricostatic drugs and anti-inflammatory drugs, the median price of prednisolone was 1.2PKR ranging from 0.15PKR to 3.03PKR while the median price and price range of Allopurinol and Febuxostat was 3.5PKR ranging from 1.2PKR to 4.63 and 16.5PKR ranging from 9.45PKR to 40PKR respectively based on the interpretation as shown in Figure 4.2.

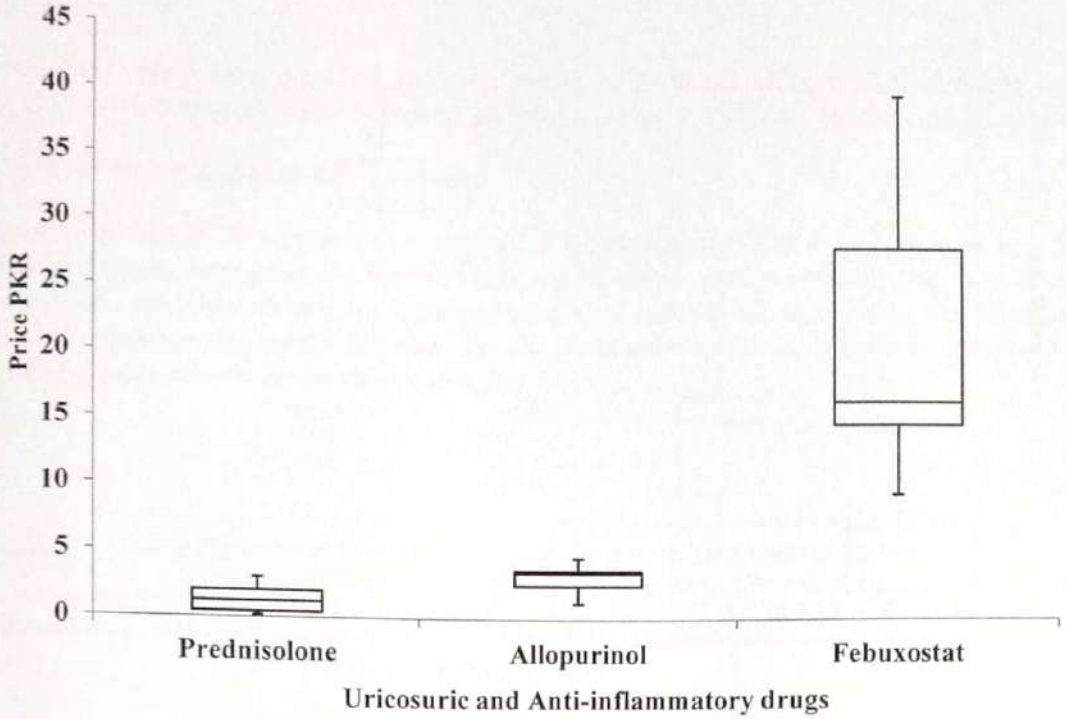

Figure 4.2 Whisker plot for Uricosuric and anti-inflammatory drugs

Among non-selective anti-inflammatory drugs naproxen shows highest median price of 7.15PKR ranging from 2.81 PKR to 71.6PKR. and Indomethacin shows the lowest median price 0.46PKR ranging from 0.2 to 0.6PKR. Median price of aspirin is 0.69PKR ranging from 0.03PKR to 2.08PKR. Diclofenac median price was 3.5PKR with minimum price 0.3 to maximum price 11.95 PKR. Mafenamic acid and ibuprofen has median price 0.75PKR (range <0.1 to 8.75PKR) and 0.97PKR (range <0.1 to 43PKR) respectively as shown in figure 4.3.

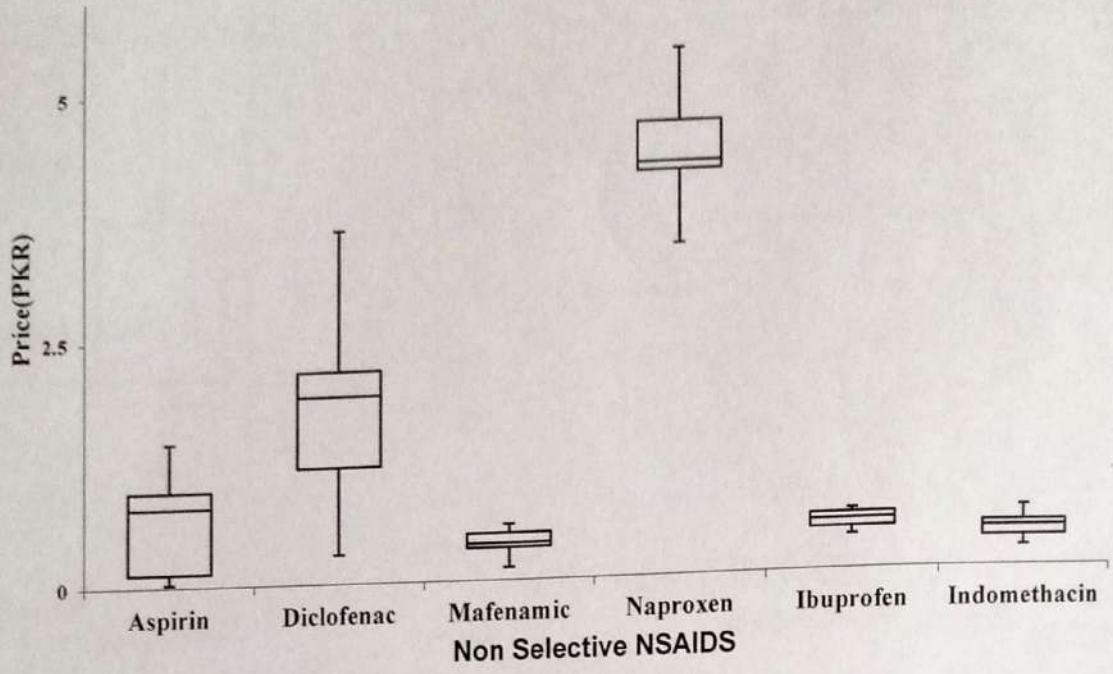

Figure 4.3 Whisker plot for Non-selective NSAIDS

For selective NSAIDs Etoricoxib and Celecoxib, Etoricoxib shows no price variation as price of all brands is same with a median price of 10PKR while Celecoxib has median price 6 with a price range of 2.5PKR to 23PKR as shown in Figure 4.4.

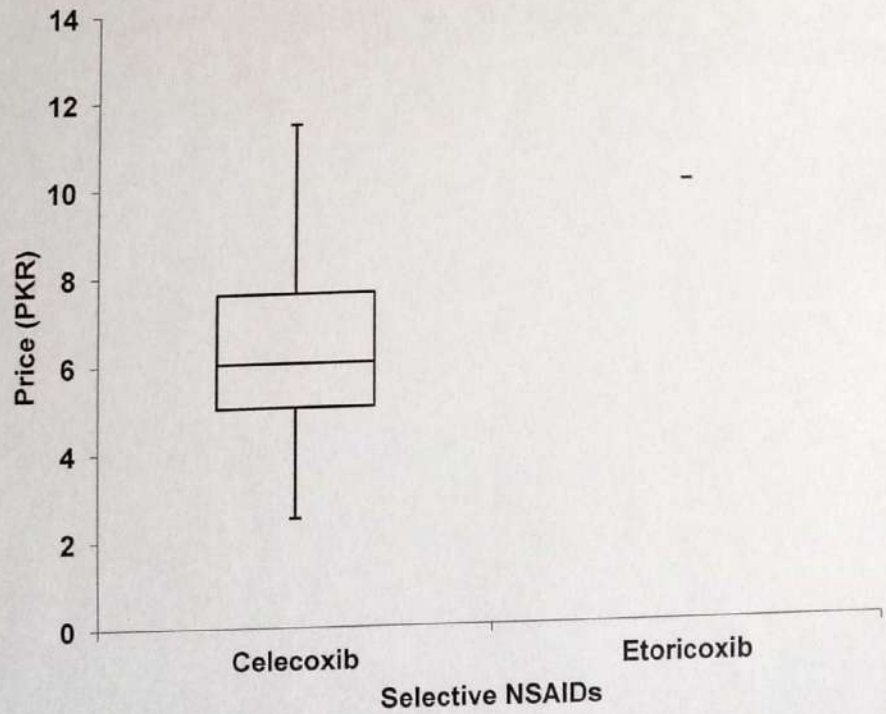

Figure 4.4 Whisker plot for selective NSAIDS

4.3 A Systematic Review on traditionally used herbs against hyperuricemia and gout

4.3.1 Literature Search:

Different data bases have been searched for time period of 2000 till January 2021 and this resulted in database of 3017 articles from electronic database of Google Scholar, PubMed, Science direct and Cochrane.

4.3.2 Database screening and selection outcome:

Database search yielded 3017 articles after removal of duplicates only 2008 articles were left. Title and abstract of 2008 articles were accessed for the study out of which 1601 were excluded, 407 articles were selected for full text reading. 398 articles were excluded after reading full text due to unavailability of full text, publication language, ineligible full text, non-RCT, unable to follow eligibility criteria. Finally, 9 studies were included in this review as shown in figure.

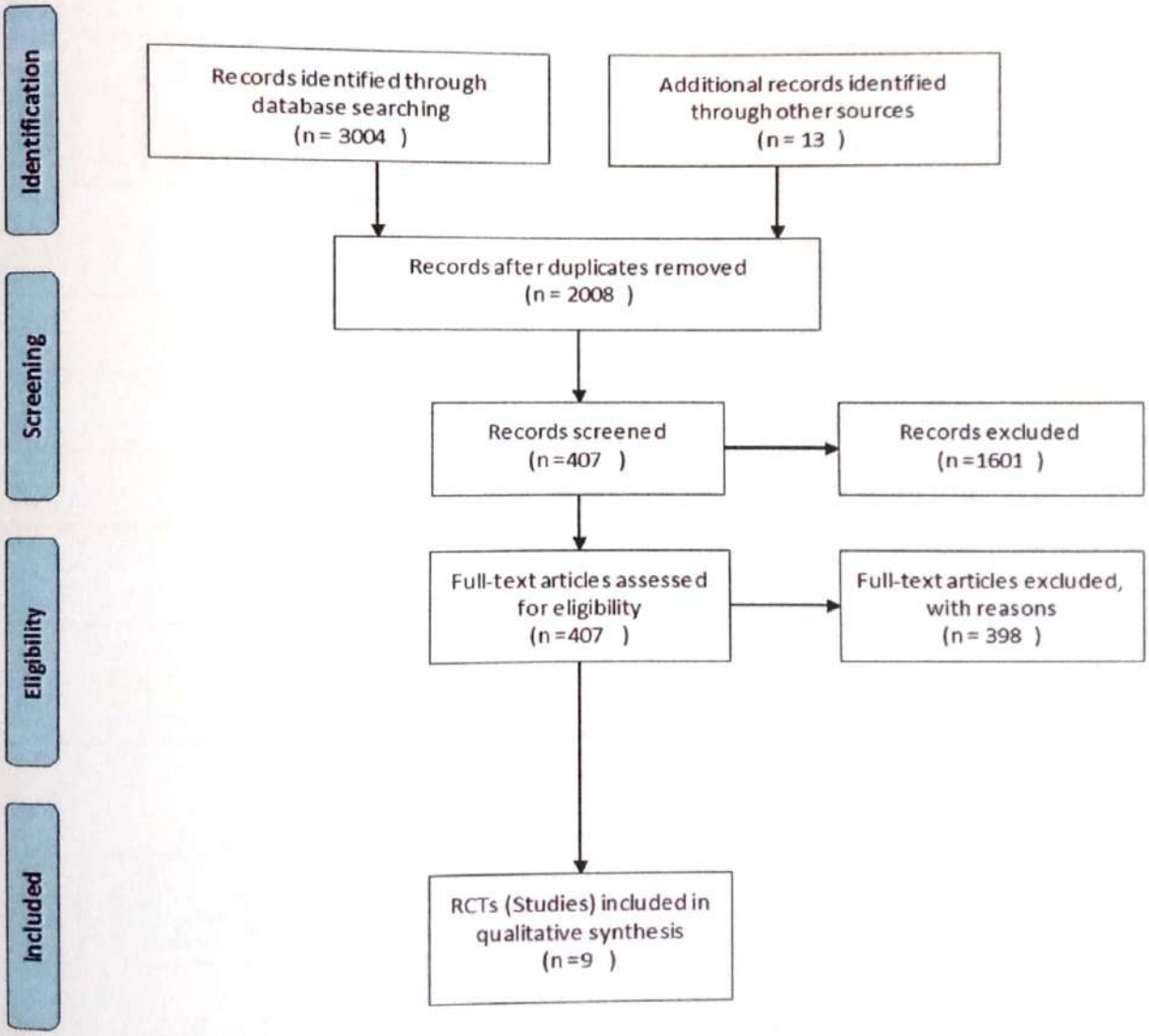

Figure 4.5 Prisma flow diagram

4.3.3 Data Extraction:

Data was extracted in such a detailed and organized way that it contains all the useful and relevant information from all the articles selected previously. Two different sheets were prepared which consist of patient characteristics and study characteristics along with outcomes as shown in table.

Table 4.12 Study characteristics of RCT

Sr No.	Author	Year	Country	Study design	Randomized / Not randomized	Type of Allotment in groups	Allocation ratio	Sample size	Study period	Follow-up period	Intervention	Composition	Comparator	outcomes	Title	ADR
1	**Marina Hirano**	2017		placebo-controlled double-blind cross-over trial	randomized		01:01	39	4week		100 mg of LCE	LCE was obtained by aqueous ethanol extraction from the flowers of Chrysanthemum indicum.LCE (commercial name: Kiku Flower Extract-P; Lot. T-519) contained 10% luteolin	Placebo capsules with the same appearance as the LCE capsules that contained 100 mg of dextrin .	significant decrease of serum uric acid was observed after LCE ingestion in the subjects with a baseline uric acid level of 5.5 to 7.0 mg/dL.	Luteolin-rich chrysanthemum flower extract suppresses baseline serum uric acid in Japanese subjects with mild hyperuricemia. Integr	

Results

2	**Ren, Shuang**	2020	China	n open-label, randomized, controlled, and parallel-group study	randomized	random	01:01:01	90	7days	7days	Western–medicine–basic treatment, including low-purine diet, drinking water more than 2000 mL/d, three times loxoprofen (60mg each time) and NAHCO3 (1g each time) per day orally+T2 receive	CQBG consist of Cortex Phellodendri and Herba tuberculate speranskia as the main components	Western–medicine–basic treatment, including low-purine diet, drinking water more than 2000 mL/d, three times loxoprofen (60mg each time) and NAHCO3 (1g each time) per day orally.T1 group received an external application of	A significant decline in the pain duration of the target joint.s welling score on day 7 was significantly lower. a significant improvement was seen in thickness of the synovium of target joints after the treatment,	Effects of external application of compound Qingbi granules on acute gouty arthritis with dampness-heat syndrome: A randomized control trial		

											d test drug Qingbi external application of 30 gCQBG		diclofenac diethylamine emulgel			
3	**Mahmood Ahmad**	2013	Pakistan	Randomized single blind experimental design	randomized	random	N/A	200	3month	No	10 drops TDS of tinctures of Ocimum sanctum Linn	tinctures of Ocimum sanctum Linn	10 drops TDS of tinctures of Ledum palustre Linn	Ledum palustre Linn has better efficacy in decreasing serum uric acid than Ocimum sanctum Linn in both males and females.	The effect of ocimum sanctum and ledum palustre on serum uric acid level in patients suffering from gouty arthritis and hyperuricaemia	

Results

4	**Shi Xin-de**	2008	China	randomized and controlled clinical trial	randomized	random	N/A	107	2weeks	N/A	600 mL decoction of Simiao Pill which was taken orally in 3 portions, once daily.	Rhizoma Atractylodis 20 g, Cortex Phelloden dri 20 g, Semen Coicis 30 g, Radix Cyathulae 30 g, Rhizoma Smilacis Glabrae 30 g, Caulis Lonicerae 20 g, Radix Paeoniae rubra 20 g, Gypsum Fibrosum 50 g, Rhizoma Anemarrhenae 20 g, and Ramulus Cinnamomi 5 g.	ndomethacin at 50 mg per time, 3 times a day. When the symptoms improved, the dose was reduced to 25 mg, 3 to 4 times a day. Benzbromarone was administered at 500 mg per time, after breakfast, once per day.	The clinical efficacy of Group I, Group II, Group III and the control group was 96.3%, 96.3%, 96.8% and 68% respectively.	Randomized and controlled clinical study of modified prescriptions of Simiao Pill in the treatment of acute gouty arthritis	
5	**Song En-feng**	2008	China	clinical trial	randomized	randomized by digital table	01:01	200	4weeks	N/A	Weicao Capsule	WCC, which consisted of herbs	control group were treated	The level of ¡2-microgl	Clinical effect and action	total, 17 cases did show adverse

						into two groups equally					orally three times a day, 2 capsules every time.	of clematis root, cassia seed, crude rhubarb, lysimachia, motherwort,	with Tongfengding Capsule orally three times a day, 2 capsules every time.	obulin got lowered significantly, blood urea nitrogen, serum creatinine and the clearance rate of creatinine,The total effective rate was 87% in the treated group, which was superior to that in the control group (62%,	mechanism of Weicao Capsule in treating gout	reactions like nausea, vomiting and poor appetite during the treatment period

Results

6	**Chen Qian**	2009	China	Clinical trial	N/A	N/A	N/A	78	6weeks	N/A	Allopurinol tablet was given to group in the dosage of 100 mg three times a day.treated group was given additional retention enema of Chinese herbal decoction once a day	The decoction used for enema consisted of crude rhubarb 30 g, calcined oyster shell 50 g, waterplantain rhizome 30 g, red sage root 15 g, sophora flower 30 g, aconite root 15 g, and scullcap root 30 g. It was boiled down to 500 mL of decoction. In enema, 150 mL of the decoction was used each time for high enema	Allopurinol tablet was given to group in the dosage of 100 mg three times a day	treated group, significant improvements were shown in terms of blood levels of triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), as well as 24 h U-mAlb, pH in urine, and 24 h	Clinical study on treatment of hyperuricaemia by retention enema of Chinese herbal medicine combined with allopurinol	No any adverse reaction

															Results				
															(20-30 cm) and reserved there for over 60 min		amount of urine.Levels of SUA, BUN and SCr, as well as CCr were significantly improved after treatment in the treated group but in the control group, these indices, except SUA were improved insignificantly		

														the prespecified non-inferiority margin of -0.5×10^{9}/L), and C-reactive protein (treatment difference within the prespecified non-inferiority margin of -1.0 mg/L). The Chuanhu anti-gout mixture was associated with a		

														better effect in relieving pain in the affected joint, but it was not associated with changes of swelling and limitation scores of the affected joint, or with blood urea nitrogen, blood sugar, triglycerides and total cholesterol, compar		

Results

														ed to Colchicine		
8	**Zhijun Xie**	2017	China	Clinical trial	multicenter, randomized, placebo-controlled, and double-blind trial	random	01:01	210	12-week	—	CoTOL (each 2 packs a day)	Rhizoma smilacis Glabrae (Smilax glabra, Tufuling) 30g, Rhizoma dioscoreae collettii (Dioscoreatokoro Makino, Bixie) 30g, Curcuma longa (turmeric 12g, Jianghuang), Herba siegesbeckiae 18g(Glandularstalk St.Paul's Wort herb, Xixiancao), and	The control group patients were treated with a placebo consisting of 20g each of charred millet sprout (Millet sprout, JiaoGuya) and fructus hordei germinatus (Barley sprout, Maiya), 12g of charred fructus crataegi	CoTOL reduced sUA levels and effectively prevented acute arthritis recurrence in intercritical and chronic gout without serious adverse event	Hypouricemic and arthritis relapse-reducing effects of compound tufuling oral-liquid in intercritical and chronic gout: a double-blind, placebo-controlled, multicenter randomized trial	fewer leucopenia incidences

Results

												Rhizoma corydalis 18g(Yanhusuo, Yanhusuo), Semen coicis 30g (coix seed, Yiyiren), Loranthus parasiticus15g (Chinese taxillus twig, Sangjisheng), and Stigma maydis 15g (corn silk, Yumixu).	(Chinese Hawthorn fruit, JiaoShanzha), and 3g of edible bitter principle, which each have no therapeutic effects on gout			

Results

9	**Xiao Ning Yu**	2018	China	Clinical trial	pilot randomized controlled trial	random	01:01:01	72	4weeks	—	receive either YWF decoction, YWF + gypsum 15g decoction, orally three times daily (100 mL each time) for four weeks.	Earthworm 10g,Cardamon 6g,Cortex Phellodendri 10g,Atractylodes 9g,coix seeds 20g,cyathula 10g	allopurinol.The starting dose of allopurinol was 100 mg day−1 in week 1 and increased to 200 mg during weeks 2–4.	YWF decreased uric acid.but there is no diiference in uric acid upon adding gypsum	Yellow-dragon Wonderful-seed Formula" for hyperuricemia in gout patients with dampness-heat pouring downward pattern: a pilot randomized controlled trial	No any adverse reaction

Table 4.13 Study Population characteristics

Author	Marina Hirano		Ren, Shuang	Mahmood Ahmad	SHI Xin-de	SONG En-feng	CHEN Qian	YanGang Wang,	Zhijun Xie	Xiao Ning Yu
Praticipants	For the single-dose study, the 20 subjects were allocated to 2 groups so that the average age and uric acid level were similar.Subjects enrolled with fasting serum uric acid level 5.5 to 8.0 mg/dL and an increase of serum uric acid after	For the repeatedadministration study, the 30 subjects were allocated to 2 groups from the highest value to lowest uric acid value.healthy men aged 20 years or older were recruited from among the employees of Oryza Oil & Fat Chemical Co. Ltd. who freely gave consent to the study.subjects were grouped so that the average age was similar in each group. Uric	Patient with one or more acute gout attacks and hyperuricemia aging 18-70	Patient with attrhritis ,hyperuricemia,gouty arthritis	Patients with hyperuricemia and gouty arthritus includeing primary and recurrent cases	Patients with gout	Patients with hyperuricemia where uric acid > 416micromol/L in males and >357micromol/L in females	Patients with gout as per ACR criteria and onset of disease was less than 48hr	Patients with gout and hyperuricemia as per ACR	Patient with hyperuricemia and heat dampness pouring heat downward

		ingestion of the test meal was confirmed	acid levels ranged from 4.5 to 7.8 mg/dL .								
Sample Size	Screened	39	39	90	200	120	200	78	176	332	72
	Randomized	20	30		100		200	78	176	210	72
	Completed Study	20	26	84	100	107	188	78	164	173	62
Male;n%		100	100		60	93.45794	94.5	93.58974		100	
Age (years)	Range	22-71	22-71	18-70	NA	23-82	21-70	38-68		18-60	18-70
	Median										
	Mean					54.5	46	51.5			
Ethnicity		japanese	japanese	Chinese	Asian	China	China	china	China	China	China

4.3.4 Risk of bias Assessment:

75% of studies show low risk of bias in allocation concealment and incomplete outcome data. 60% studies show low risk of bias in Blinding of participants and personnel, blinding outcome assessment and selective reporting while the risk of bias in random sequence generation was very low up to 90% as shown in figure.4.6

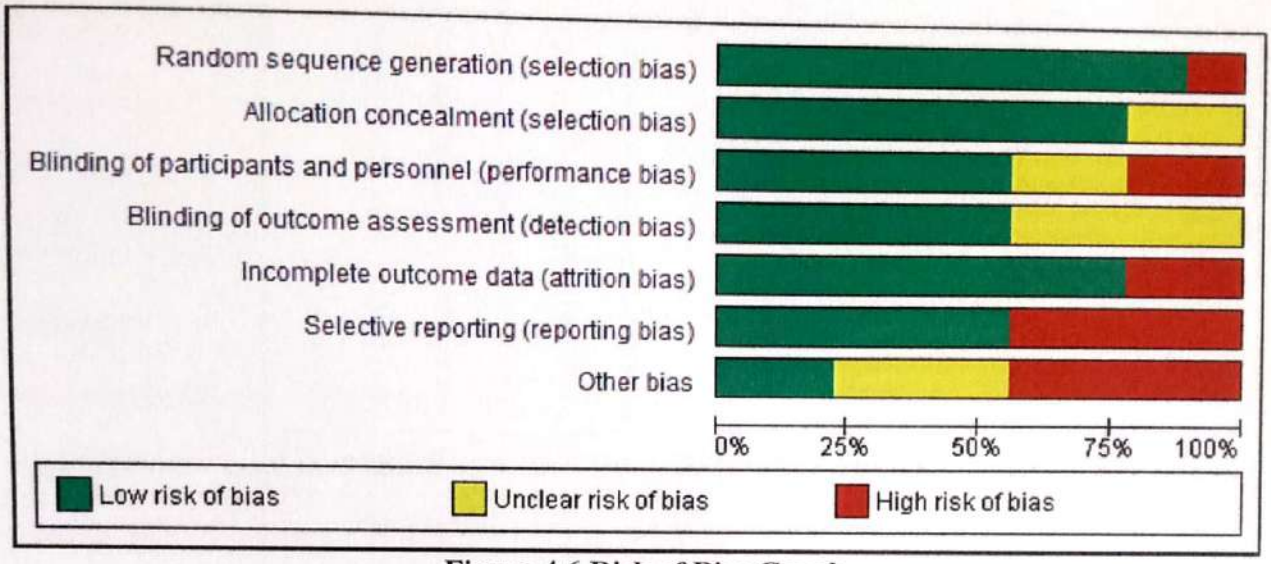

Figure 4.6 Risk of Bias Graph

Summary of risk of bias is as shown in figure 4.7

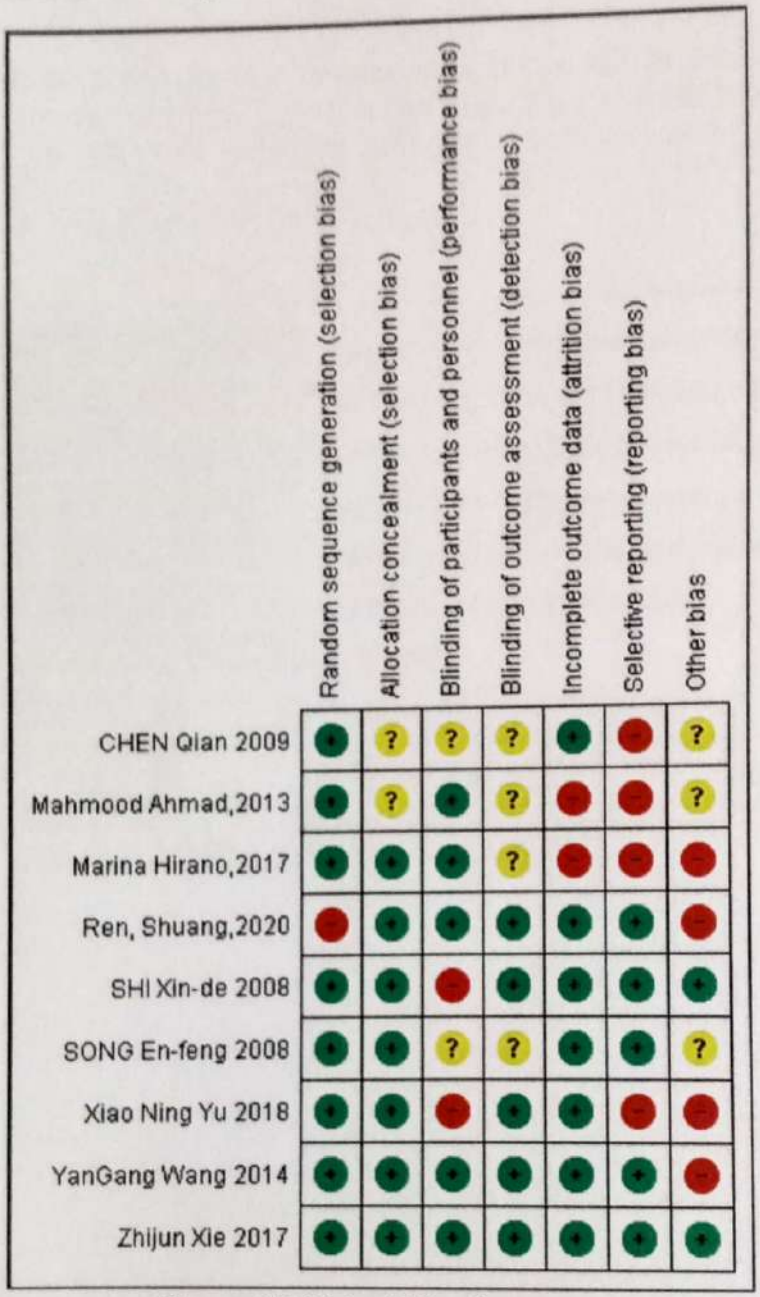

Figure 4.7 Risk of Bias Summary

Description of included studies:

Among all the studies included in this systematic review n=9 ((Ahmad *et al.* 2013; Chen *et al.* 2009; Hirano *et al.* 2017; Li *et al.* 2008; Ren *et al.* 2020; Song *et al.* 2008; Wang *et al.* 2014; Xie *et al.* 2017; Yu *et al.* 2018)) , three are double blind placebo controlled randomized trial n=3 ((Hirano *et al.* 2017);(Wang *et al.* 2014; Xie *et al.* 2017) ,one is single blinded randomized controlled trial n=1 (Ahmad *et al.* 2013)all remaining n=5(Chen, Ma et al. 2009, Ren, Meng et al. 2020, Li, Qian et al. 2008, Song, Xiang et al. 2008,(Yu *et al.* 2018) are randomized controlled trials. All the studies were conducted in Asian region.

Six of the studies (n=6)(Marina Hirano et al. 2017; (Ren *et al.* 2020)Shi Xin-de et al. 2008; Song En-feng et al. 2008; YanGang Wanget al. 2014; Xiao Ning Yu et al. 2018)has duration of intervention less than or

equal to four weeks while other three studies n=3 ((Ahmad *et al.* 2013; Chen *et al.* 2009) (Xie *et al.* 2017)has treatment duration more than 4 weeks.

Intervention classified into topical ((Ren *et al.* 2020); with Cortex phellodendri and Herba tuberculate speranskia as major components and Chen Qian et al. 2009; rhubarb

30 g, calcined oyster shell 50 g, waterplantain rhizome 30 g, red sage root 15 g, sophora flower 30 g, aconite root 15 g, and scullcap root 30 g as main components) and oral dosage form(Marina Hirano et al. 2017; Shi Xin-de et al. 2008; Song En-feng et al. 2008; YanGang Wanget al. 2014; Xiao Ning Yu et al. 2018; Mahmood Ahmad et al, 2013; Chen Qian et al. 2009; Zhijun Xie et al. 2017) as described in table 4.12 study characteristics of RCT while participant characteristics are shown in table 4.13

Intervention and effectiveness:

All the 9 interventions included in the review were effective in one or the other way. Four studies (Marina Hirano et al. 2017; Mahmood Ahmad et al, 2013, Zhijun Xie et al. 2017; Xiao Ning Yu et al. 2018) reduced serum uric acid significantly.

Supplements:

Luteolin-rich chrysanthemum flower extract:

LCE was obtained by aqueous ethanol extraction from the flowers of Chrysanthemum indicum.LCE (commercial name: Kiku Flower Extract-P) contained 10% luteolin. 100mg of LCE decreased uric acid significantly.

Simiao Pill:

Simiao pill consist of Rhizoma Atractylodis 20 g, Cortex Phellodendri 20 g, Semen Coicis 30 g, Radix Cyathulae 30 g, Rhizoma Smilacis Glabrae 30 g, Caulis lonicerae 20 g, Radix Paeoniae rubra 20 g, Gypsum fibrosum 50 g, Rhizoma anemarrhenae 20 g, and Ramulus cinnamomi 5 g. 600ml decoction taken three times a day decreased seum uric acid and has efficacy of 96%.

Weicao Capsule:

WCC, which consisted of herbs of clematis root, cassia seed, crude rhubarb, lysimachia, motherwort. Weicao Capsule taken orally three times a day, 2 capsules every time lowered BUN, Serum creatinine with efficacy of 87%. total, 17 cases did show adverse reactions like nausea, vomiting and poor appetite during the treatment period.

Retention enema of Chinese herbal medicine:

The decoction used for enema consisted of crude rhubarb 30 g, calcined oyster shell 50 g, waterplantain rhizome 30 g, red sage root 15 g, sophora flower 30 g, aconite root 15 g, and scullcap root 30 g. It was boiled down to 500 mL of decoction. In enema, 150 mL of the decoction was used each time for high enema (20-30 cm) and reserved there for over 60 min. treated group, significant improvements were shown in terms of blood levels of triglyceride (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), as well as 24 h U-mAlb, pH in urine, and 24 h amount of urine.Levels of SUA, BUN and SCr, as well as CCr were significantly improved after treatment in the treated group but in the control group, these indices, except SUA were improved insignificantly

Chuanhu anti-gout mixture:

It consists of Chlorogenic acid: 205.6 μg/ml 2: Loganin: 36.2 μg/ml 3: Resveratrol: 149.2 μg/ml. Chuanhu anti-gout mixture given 250 ml orally daily. Chuanhu anti-gout mixture was non-inferior to Colchicine in lowering the recurrence rate (treatment difference within the prespecified non-inferiority margin of 15%), white blood cell count (treatment difference within the prespecified non-inferiority margin of -0.5×109/L), and C-reactive protein (treatment difference within the prespecified non-inferiority margin of -1.0 mg/L). The Chuanhu anti-gout mixture was associated with a better effect in relieving pain in the affected joint, but it was not associated with changes of swelling and limitation scores of the affected joint, or with blood urea nitrogen, blood sugar, triglycerides and total cholesterol, compared to Colchicine. Chuanhu anti-gout mixture was associated with significantly fewer adverse events (especially diarrhea) and lower levels of aspartate aminotransferase, alanine aminotransferase, creatinine and blood uric acid compared to Colchicine.

CoTOL:

It consist of Rhizoma smilacis Glabrae (Smilax glabra, Tufuling) 30g, Rhizoma dioscoreae collettii (Dioscoreatokoro Makino, Bixie) 30g, Curcuma longa (turmeric 12g, Jianghuang), Herba siegesbeckiae 18g(Glandularstalk St.Paul's Wort herb, Xixiancao), and Rhizoma corydalis 18g(Yanhusuo, Yanhusuo), Semen coicis 30g (coix seed, Yiyiren), Loranthus parasiticus15g (Chinese taxillus twig, Sangjisheng), and Stigma maydis 15g (corn silk, Yumixu). CoTOL given 2 packs a day.

Yellow-dragon Wonderful-seed Formula:

It contains Earthworm 10g, Cardamon 6g, Cortex Phellodendri 10g, Atractylodes 9g, coix seeds 20g, cyathula 10g. receive either YWF decoction, YWF + gypsum 15g decoction, orally three times daily (100 mL each time) for four weeks. YWF decreased uric acid.but there is no difference in uric acid upon adding gypsum.

4.4 Factors affecting the adherence of patients with Uremic therapy

A total 52 patients with a diagnosis of hyperuricemia and gout were included in the study. The mean age of population was 48 ±10 year and 71.2% were female. Patients were with the BMI 29.2±5 and mean uric acid 7±1 g/dl. Over the period of 6 months patients dispensed with uric acid lowering agent were included. Common comorbidities were hypertension 40.4%, diabetes 28.8%, GIT disorders 34.6%, dislipidemia 11.5%, Kidney disease 2%, Cardiovascular disease 19.2% and 5.8% with smoking habit as described in table.

Table 4.14 Demographics of patients for adherence of medication

Demographics		n	%
Age	20-40	13	25
	41-60	36	69
	61-80	3	6
Gender			
	Female	37	71.2
	Male	15	28.8
BMI			29.2±5.5

Employ status	employed	19	36%
	unemployed	33	63.50%
Marital status	married	47	90.40%
	unmarried	3	5.80%
	divorced	1	1.90%
	widow	1	1.90%
Education	Not educated	9	17.3
	primary	6	11.5
	matric	8	15.4
	inter	5	9.6
	graduate	20	38.5
	postgraduate	4	7.7
Comorbidities	Cardiovascular disease	10	19.20%
	Cerebrovascular disease	4	7.7
	Kidney Disease	1	1.90%
	Diabetes	15	28.8
	Hypertension	21	40.4
	Dislipidemia	6	11.5
	GIT Disorder	18	34.6
	Smoke	3	5.8

Medicine	Allopurinol 100	10	19.2
	Allopurinol 300	10	19.2
	Febuxostat 40	22	42.3
	Febuxostat 80	10	19.2

Use of urate lowering agent was common in gout and hyperuricemia (Allopurinol 100mg 19.2%, Allopurinol 300mg 19.2 %, Febuxostat 40mg 42.3% and Febuxostat 80mg 19.2%.

Adherence score calculated was as 0 (high adherence) for 3.8%, 1-2 (moderate adherence) for 69% and 3 or above (low adherence) was 27% as described in figure 4.8.

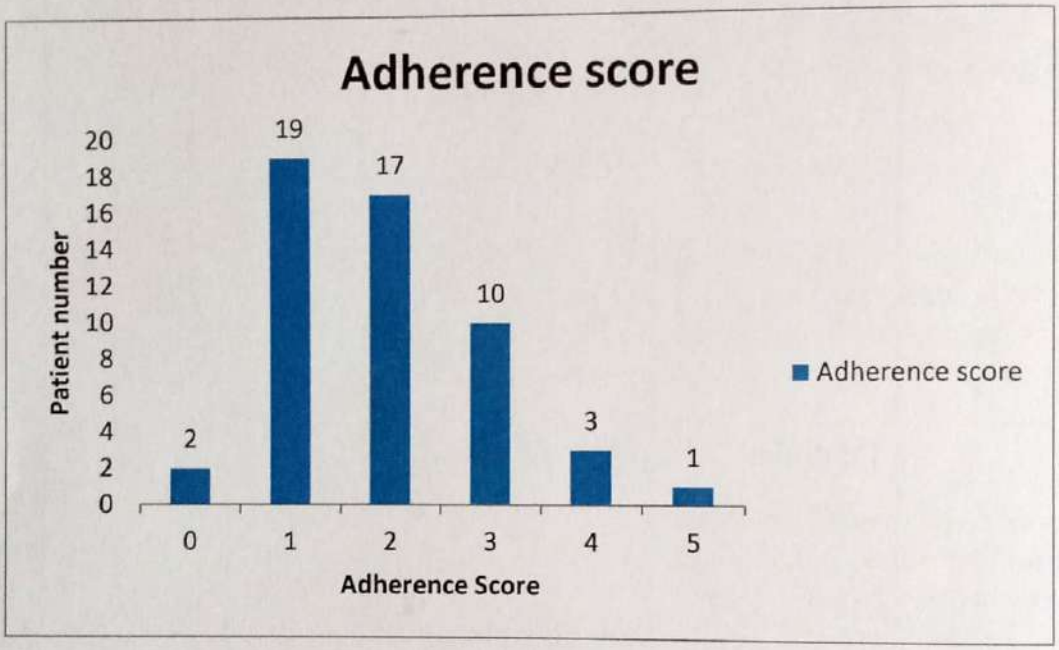

Figure 4.8 Adherence Score of Patients

Linear Regression analysis showed correlation of adherence score with different comorbid conditions. Patients have low to negligible adherence effect having GIT disorder as regression score was lowest -0.02 with a confidence interval of 95%.Patients having dyslipidemia and kidney disease have 10 to 15% higher adherence rate as regression score is –0.10 and - 0.15 respectively as shown in table

Table 4.15 Regression analysis of Comorbid condition

Parameter	Beta In	t	Sig.
Smoke	.078[b]	.560	.578
GITDisorder	-.015[b]	-.087	.931
Dislipidemia	-.102[b]	-.669	.507
Hypertension	-.080[b]	-.498	.621
Kidney Disease	-.148[b]	-1.090	.281

Diabetic patients were on the highest adherence rate as the regression score was -0.64. So, diabetic patients were 64% more adherent among all other diseased patients. With the increase in age the adherence rate has minimum to negligible change as shown in table.

Table 4.16 Regression analysis for Diabetic Disease

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	2.108	.170		12.420	.000	1.767	2.449
	Diabetes Disease	-.641	.316	-.276	-2.030	.048	-1.276	-.007

CHAPTER 5
DISCUSSION

Hyperuricemia a metabolic disorder leads to many complications (nephrolithiasis, diabetes, cerebrovascular disease) and absence from the work. Hyperuricemia occurs due to either high intake of purine rich diet or under excretion of uric acid. It occurs mostly in humans as they lack uricase enzyme (present in animals) which converts uric acid to a soluble form for excretion (Álvarez-Lario and Macarrón-Vicente 2010; Hayashi *et al.* 2000). 5-12% of Hyperuricemic patients develop gout (Lin *et al.* 2000). Gout is a purine metabolism disorder which involves deposition of monosodium urate crystals in peripheral joints and soft tissues when uric acid level rise above the threshold ultimately leading to the inflammation of the specific joints (de Oliveira and Burini 2012). Different types of drugs are used in the symptomatic hyperuricemia and gout. Among them uricostatic drugs inhibit the xanthine oxidase enzyme ultimately inhibiting production of uric acid. Allopurinol is the drug of choice for over production of uric acid (FitzGerald *et al.* 2020). Although it is very efficacious and well tolerated yet it has many adverse effects including gastrointestinal intolerance, bone marrow suppression, hepatic toxicity and skin rash. Nonsteroidal Anti-inflammatory drugs are also used for gout attacks but these drugs cause GIT intolerance and peptic ulcer. Keeping in view above mentioned side effects, alternative medicines free of side effects are of great interest for the management of hyperuricemia and gout.

Herbal medicines are used for restoration of function and enhancing quality of life. In present study Uripro having seven herbs in combination work by integrating action of individual herb. Uripro decreased uric acid, reduced pain and inflammation. Among lab parameters WBCs, ESR decreased, hemoglobin increased, and serum creatinine remained the same.

Colchicum has been used as antigout from centuries as it relieves pain, inflammation and it also shortens duration of pain (Akhtar 2018). Colchicum luteum which is a perennial herb with bitter taste small size and dark color. Dried corm of colchicine consists of 0.6% of alkaloid colchicine which amorphous readily soluble in alcohol, water or chloroform.It is used extensively in medicine for gout treatment as it relives inflammation and shorten therapy duration. Colchicine suppresses MSU and activation of NLRP3 inflammasome which suppresses activation of caspase-1 involved in release of IL-1B and IL18 (Akhtar 2018) ,(Slobodnick *et al.* 2018). This inflammation reduction property could be contributing to relive gout and hyperuricemia symptoms.

Glycyrrhiza glabra (common name mulhatti) a perennial shrub is ancient herb with taproot that comprises of glycyrrhizin which is a saponin with antiinflamatory acivity not less than hydrocortisone. Glycyrhizin inhibits phospholipase A2, an enzyme that is involved in inflammation process. Glycyrrhizic acid also inhibits activity of cyclooxygenase and formation of prostaglandin ultimately inhibiting platelet aggregation which are involved in inflammation process (Kaur *et al.* 2013). This inflammation reduction property must be adding to the symptomatic treatment of gout.

Zingiber officinale (ginger) is known for its phytochemicals as It consists of saponins, alkaloids, tannins, flavonoids and glycosides. Major components are gingerol, shagole, gingiberene. Rhizome of Ginger has antioxidant properties on DPPH (α, α-diphenyl-β-picrylhydrazyl), nitric oxide and flavonoid in it has xanthine oxidase inhibition property. Ethanol compound of ginger inhibits xanthine oxidase enzyme similar to that of allopurinol (Muthusamy and Jeyabalan 2019).This xanthine oxidase inhibition property could be decreasing uric acid level.

Wathania somnifera is herb with many bioactive compounds like withaferin A , withanolide D. beta-sisterol, Anaferine, anahygrine, chlorogenic **acid**.(Akram *et al.* 2011). It contains several alkaloids,

withanolides, reducing sugars and flavonoids. The powder of roots of Wathania somnifera decreased the release of enzyme from PMNL cells that was induced by the monosodium urate crystals thus reducing inflammatory response (Rasool and Varalakshmi 2006). This could be the possible mechanism of reducing inflammation in the symptomatic hyperuricemia and gout.

Piper nigrum commonly known as black pepper is known for its use as spices around the world. It has wide pharmacological properties. It has active ingredients Piperine, pellitorine, kusunokinin and piperlongumine. Piperine inhibits activity of 5-lipoxygenase and COX-1(cyclooxygense-1). Piperine has anti-inflammatory, immunomodulatory, neuroprotective, cardioprotective.and anticancer effect. This could be the possible mechanism of pain resolution and inflammation reduction (Tasleem *et al.* 2014; Turrini *et al.* 2020).

Piper longum commonly known as long pepper is known for its bioactive components and its use as spice.It contains volatile oil, protein, alkaloids and saponins. Major alkaloids are Piperine, piperlonguminine, Piperlongumine and trimetoxycinnamate. Piperine inhibits COX-1 and lipoxygenase, thus providing analgesic and anti-inflammatory effect.Moreover it is anti-asthmatic, immunomodulatory and hepatoprotective. These properties are adding to the effect of Uripro (Khushbu *et al.* 2011). *Boerhavia diffusa commonly known as punarnava consit of many phytochemicals* isoflavonoids, flavonoids, xanthones, purine nucleoside, lignans, and steroids. Methanol extract in it have antioxidant, cytotoxic activity ,anti-inflammatory and thrombolytic(Mishra *et al.* 2014). activity.

Rational drug prescribing is of much importance specifically in different age groups and because of limited healthcare resources. All prescribers while prescribing must consider cost-effectiveness of medicine due to continuous rise in cost of medicine (Maxwell 2009).According to WHO (the World Health Organization) estimation half of the medicines are not prescribed properly and half of the patients don't follow their prescription properly. WHO has made strategy to encourage rational drug use. This strategy is to assist nations in developing a national programme for the rational drug use (Organization 2008).Medicine prescribing from a limited list available can decrease prescription errors and irrational drug use therefore WHO has devised an essential medicine list to address this issue (Reidenberg 2009). Doctors have poor knowledge of medicines cost. Overestimation of inexpensive drugs price and underestimation the expensive drug price by the doctors due this lack of medicine cost knowledge makes a huge difference in prescribing a cost-effective medicine (Allan *et al.* 2007). There is no proper method to guide prescribers about the cost of the medicine in Pakistan. Only medical representatives guide doctors about the cost of the medicines and their expenditure (Saeed *et al.* 2019).Therefore we are in dire need of a study that pay attention towards the cost analysis of various available products specially in this region where there are limited resources.

The aim of current study is to figure out the number of brands registered in Pakistan and the difference in the prices of these oral anti-gout and anti-hyperuricemic drugs. Study shows that there is huge price variation among different brands. Current study shows that there is huge price variation among different brands. 31 different formulations show a price variation from 0% to 14400% while 5 formulations had 0% price variation ,6 formulations showed a price variation of <100% , 9 formulations were with the price variation <1000% and other 10 formulations had price variation above 1000%. Ibuprofen 400mg showed the highest price variation (14400%) while Etoricoxib, two of aspirin formulation (100mg,500mg), colchicine, one of febuxostat (120mg) formulation and one formulation of naproxen (50mg) did not show any price variation (0%).

Different registered brands have high price variation. In Pakistan DRAP (Drug regulatory authority of Pakistan) which works under federal government was established in 2012. This regulatory authority is responsible for the fixing the prices of medicine (Lee *et al.* 2017). DRAP has taken measures to control the

prices of medicines but these measures were opposed by pharmaceutical organization because wholesale mark-up was very low from 2% to 10% (Cameron *et al.* 2009; Mendis *et al.* 2007).The first pricing policy for Pakistan was set in 2015. According to Drug Pricing Policy 2015 of Pakistan new drug price will be set as per the average of prices already set in in Bangladesh and India and if the specific drug is not available in these countries then the price will be set according to the lowest price available for that drug in developed countries like Australia, New Zealand, UK. It also contains the originator brand price reduction concept of up to 30% reduction in three stages annually. Moreover this policy also correlates annual price increase with Pakistan Bureau of Statistics announced CPI (Consumer Price Index), according to which the suggested increase in price was 1.43% for scheduled medicines and 2% for non-scheduled medicine. In 2018 another national drug pricing policy (NDPP) was launched to amend the previous policy in terms of price hike issues, essential medicine list and annual price increase criteria. As per this NDPP 2018 the annual increase in prices criteria was set up to 4% and 6% of CPI for scheduled drugs and non-scheduled drugs respectively. In this policy 414 drugs from Essential medicine list were included in scheduled drugs while in 2015 policy only 160 drugs were included in schedule category. Schedule drugs are those which are placed under rigorous price control. As per this policy of 2018 price of new product is determined as that of highest priced available generic while in 2015 policy price is set to the average price of available brands. This step can decrease the affordability of product (Areeba and Ali 2021; DRAP. 2015; DRAP.).

National Essential Medicine list of Pakistan doesn't consist of all anti-gout and anti-hyperuricemic drugs. It consists of only two drugs under this category one for the palliative care namely Ibuprofen and other under anti-gout category that is Allopurinol 100mg (DRAP. 2020).Although allopurinol is included in the NEML, but no single OB (originator brand) was present in public healthcare facilities. Recent study suggested that only 6.8% OB in public sector and 55% in private sector are available while for the low-price generic their number is 35.5% in public and 20.3% in private. Above mentioned number far below target of WHO which is 80% essential medicine availability by 2025.Moreover prices of medicines in Lahore were very high as compared to International references prices and physicians mostly prescribe specific brands for incentive purpose (Saeed *et al.* 2019).

Doctors are the decision makers for the selection of brand of medicine. Public doctors follow National Essential Medicine List while other doctors are impacted by pharmacy market. A study suggested that in Pakistan 85.5% physicians believe that multinational medicines have more efficacy and 52.7 % physicians prescribe medicine of multinational companies. Only 37.1% doctors and 24.9% patients believe that doctors prescribe low cost medicines. Moreover doctors prescribe medicine available at near pharmacy (Husnain *et al.* 2019). This leads to low affordability of medicine for the patients. Data suggests that prices of many of the medicines rised so high that they become unaffordable by 2019. Three most unaffordable treatment in term of OB are Cardiovascular disease, ulcers and diabetes. Among this ulcer is also unaffordable in terms of low-price generics. Non communicable disease burden is very high around the world and they fill the top three slots for unaffordability aspect (Dans *et al.* 2011; Siegel *et al.* 2014).

There is huge price variation among different medicines which make them unaffordable for the common people. Unaffordability is due to no specific drug pricing formula, less local cost-effective medicines, physicians prescribing multinational medicines with high cost.(Atif *et al.* 2017).Study suggest that recently, there was above 100% price increase in medicines in Pakistan(Saleem *et al.* 2016) while the policy of annual price increase is linked to CPI and is 4% for scheduled drugs and 6% for non-scheduled drugs. Price hike to such level is illegal, Moreover essential medicines are short in supply and this can be fixed by proper by price fixation by DRAP as previously role of DRAP in this regard is ineffective (Areeba and Ali 2021) (Atif *et al.* 2019).

Increased medicine prices has led to decrease affordability and accessibility which has resulted in poor disease control due to low adherence of medication (Saleem *et al.* 2016). In LMIC medicines has become unaffordable, a recent study proposed that in Pakistan treatment with originator brand is so

expensive that it is equal to 1.4-day wages of a person while with low price generic it is 0.6-day wages of medicine. In 2006 affordability study was conducted using WHO standard method which also depicts that medicines have become unaffordable by common people (Kiani *et al.* 2007; Saeed *et al.* 2019).little research has been done on cost analysis and price variation of medicine as it is time consuming but still need of the time for cost-effective prescribing and increasing affordability of medicine so, this study is conducted to provide an overview of cost analysis and price variation among the registered drugs used for gout and hyperuricemia in Pakistan, moreover this study is valuable addition to the previous literature as no such study is available previously in this regard.

Allopathic medicines were used for the treatment of hyperuricemia and gout but they were associated with side effects So many herbal medicines came into practice. The aim of this study was to evaluate the efficacy of herbal medicine. 9 RCT were included in this review. Majority of the RCT showed low risk of bias. On the basis of this review it became clear that herbal medicine is very effective. It decreases uric acid effectively and are associated with either no or fewer side effects than allopathic medicine. This review suggests that addition of gypsum to herbal formulation does not make any difference in the effectiveness.

One herbal formulation containing clematis root, cassia seed, crude rhubarb, lysimachia, motherwort showed side effects like vomiting, poor appetite and nausea, one herbal formulation containing Chlorogenic acid, Loganin, Resveratrol showed fewer sideeefects than allopathic medicine(colchicine), while the remaining did not show any side effect.

This review is comprehensive study to compare and evaluate efficacy of different herbal therapies. In order to minimize risk of selection base a clearly predefined eligibility criteria were set. PRISMA diagram made clearly justify the included and excluded studies. Studies published in language other than English were included. This might have led to the exclusion of many relevant studies due to language barrier. Most of the studies in this review are from Asian region So, incidence of herbal use in other regions was not achievable.

The study conducted for factors affecting the adherence of patients with Uremic therapy in Lahore, Pakistan was to evaluate the factors affecting medication adherence rate in gout and hyperuricemic patients. Past studies have shown that the adherence of medication is associated with high severity of gout. However, in this prospective study the adherence association with age and comorbidities was identified. As per our findings majority of the patients were using febuxostat 40mg (42.3%). The adherence rate was 3.8% to 64%. Most of the patients had low to medium adherence rate. 69% patients were moderately adherent to the medication and 27% patients were with low adherence. Different studies show that comorbid patient have higher adherence than the non-comorbid patients. Age had negligible effect on adherence while different comorbid conditions have different impact on adherence rate. Number of comorbid conditions and relation with the adherence rate was not identified (Zandman-Goddard *et al.* 2013). Moreover, GIT disorder has negligible effect on adherence rate. Dyslipidemic patients were 10% more adherent and kidney disease patients were 15% more adherent while the highest adherence rate was of diabetic patients 64%.

As it was a questionnaire-based study so limitation to this study was that no electronic monitoring was carried out and data can be prone to bias or wrong input.

CHAPTER 6
SUMMARY

Gout is type of arthritis in which uric acid after it reaches above threshold, deposits in joints in the form of monosodium urate crystals. This deposition leads to inflammation of the joints. It occurs due to either high intake of purine rich diet or underexcretion of uric acid. It occurs mostly in humans as they lack uricase enzyme (present in animals) which converts uric acid to a soluble form for excretion. In joints deposited monosodium urate crystals attracts neutrophils and inflammatory cytokines which causes swelling of the joints. Pakistan and worldwide incidence of gout is highly prevalent. One of the major causes is lack of adherence to the allopathic treatment which occurs due to certain side effects and cost of therapy. Gout is considered to be a disease effecting quality of life.For Checking the clinical efficacy of Uripro, an open label quasi, single arm, longitudinal, interventional clinical study was performed in which 31 patients with hyperuricemia were included and advised to consume two tablets of Uripro twice a day for 30 days. Primary outcome was serum uric acid while ESR, score of the clinical outcome and serum creatinine were the secondary outcomes.

A comprehensive observational study was conducted in order to examine the cost of anti-gout drugs in Pakistan. The cost of antigouts marketed in Pakistan was derived by using Pharma guide. Information regarding registered number of brands and their prices were noted and price variation was calculated.

For systematic review Key databases Pub med, Science Direct and Google scholar amongst others were probed for a systematic search using keywords to retrieve relevant publications. A total of 3017 articles were included for the review depending on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

For identification of factors affecting adherence 52 patients who visited the community pharmacy and were prescribed with the gout or hyperuricemia medicine were included in the study. Data was collected with a questionnaire and Medication adherence was measured. Descriptive statistics was used and regression analysis was carried out to find association between adherence and factors affecting adherence.

Uripro decreased serum uric acid significantly and it has marked effects on symptom resolution. Mean serum uric acid (SUA) difference at 1st follow-up was 0.8±1.2 ranging from 0.3-1.3mg/dl which further decreased at 2nd follow up with mean SUA difference of 1.3 ±0.9 ranging from 0.75-1.9mg/dl with $p<0.05$. Pain and swelling score significantly decreased by the test drug. Moreover, this herbal formulation markedly decreased stomach issue like indigestion.

Cost analysis showed that thirteen drugs with 31 strengths which make 1307 brands are registered in Pakistan. Among 31 different formulations Price variation ranges from 0% to 14400%. Out of 31 formulations, 6 formulations showed a price variation of <100% , 9 formulations were with the price variation <1000%.Ibuprofen 400mg showed the highest percentage price variation that was 14400% (per tablet price ranging from PKR 0.1 to PKR 14.5) and colchicine 0.5mg febuxostat 120mg, aspirin 500mg and 100mg and naproxen 50mg showed no price variation.

52 patients were added in the study for measurement of adherence and factors affecting adherence. 3.8% patients were highly adherent ,65% patients were moderately adherent while 27% were with low adherence to the medication. Adherence rate decreases by 1% with the increase in age. GIT disorder patients showed minimum to negligible adherence while adherence rate was 10% to 15% higher in dyslipidemic and kidney patients respectively. Diabetic patients were with the highest adherence rate (64%).

CHAPTER 7
LITERATURE CITED

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