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Review

Fructose Increases Uric Acid Contributing to Metabolic Syndrome - Herbal, Nutritional and Dietary Strategies to Reduce Uric Acid

Michael K. McMullen *

A SARL MCMULLEN, 53 rue Blanquerie, 11300 Limoux, France; E-Mail: research@micmcmullen.se

* **Correspondence:** Michael McMullen; E-Mail: research@micmcmullen.se

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Abstract:

The metabolism of fructose by the liver produces uric acid and elevated serum uric acid levels are an independent risk factor for hypertension, metabolic syndrome, and cardiovascular disease. Fructose occurs in fruits and fruit juices, honey as well as in the sweeteners sucrose (common white sugar) and High Fructose Corn Syrup (HFCS). Dietary fructose may be considered a naturally occurring toxin because it is largely metabolised by the liver with little fructose reaching the systemic blood circulation. Uric acid is potentially toxic, as are several other molecules produced during fructose metabolism. The amount of uric acid released depends on the amount of fructose ingested, regardless of source of the fructose, i.e. whether artificial sweetener, fruit juice or whole fruit. Two-thirds of the daily production of uric acid is excreted by the kidneys in urine with the remainder is excreted by the small intestine (third kidney) in the digestive juices. It is to be expected that herbalists would have developed effective treatments for gout (resulting from elevated serum uric acid) as the symptoms are obvious, yet it may come as a surprise that these same herbs may also have a role in the treatment of the metabolic syndrome. This article reviews traditional and evidence-based herbal treatments for the reduction of uric acid together with modern nutritional treatments. Diet is also discussed, and food tables are presented which may be

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used either to avoid or treat elevated serum uric acid. Hopefully this information will also be of interest to clinicians and researchers new to this area.

Keywords

Purine content; fructose; urate excretion; hyperuricaemia; xanthine oxidase inhibitors; herbal diuretics; Dash diet; cherry juice; curcumin; green tea; activated charcoal

1. Introduction

This paper examines sources of uric acid in the diet, the disorders related to hyperuricemia and clinical approaches using diet, nutritional supplements and herbal preparations.

The impact of fructose on health has become a major research interest in the last decade [1-3] and just as purine rich food increases serum uric acid (SUA) [4] so does the consumption of fructose [5]. Fructose occurs naturally in fruits and vegetables, as well as, making up approximately 50% of the artificial sweeteners, sucrose and high fructose corn syrup (HFCS) [6].

Medium term studies, conducted over 10 weeks, comparing fructose and glucose, suggest that it is the fructose component, rather than the glucose component, of sugar and HFCS that is largely responsible for any long-term effects of artificial sweeteners on the cardiovascular and metabolic systems [7, 8]. After fructose ingestion, the acute increases in SUA are similar regardless of the source, i.e. whether the fructose is consumed in free form, fruit juice or fruit [9]. Yet, it appears that long-term consumption of foods containing fructose (NF), does not have the same cardiovascular and metabolic impact as fructose derived from artificial sweeteners (AF). After 6.7 years, higher intake levels of AF (5.4 ± 2.1 % of total energy) and total fructose (NF + AF) (9.7 ± 3.4 % of total energy) but not NF (4.3 ± 1.5 % of total energy) were related to changes of systolic and diastolic blood pressures, waist circumference, serum insulin and creatinine levels, and HDL-C [10]. This finding suggests that in the long term, the intake of fructose via foods may not have the same physiological impact as fructose derived from sweeteners. Possible reasons for this are:

1) when NF is consumed in fruits and vegetables, the non-NF food components induce satiety [11] and limit intake;
2) the non-NF components affects the impact of fructose on either the microbiota or the intestinal wall;
3) fruits and vegetables contain phytochemicals with protective effects [12].

Notably, this amount of AF, the equivalent of 10.8% of total energy as added sugars, is of the similar magnitude as the threshold level of total energy as added sugars (10%), adopted by the Dietary Guidelines for Americans [13]. So even at the recommended threshold level, added sugar/HFCS consumption may be impacting on cardiovascular and metabolic function. Studies indicate that in USA, even the lowest deciles of intakes in children, adolescents and teens, and adults, on average, exceed the recommendation for less than 10% of calories from added sugars. The primarily source of added sugar, in USA, is sugar-sweeten beverages (SSB) [14].

Traditionally, hyperuricemia, whether the result of dietary factors and/or genetic polymorphisms of the urate renal transporters, has been related to gout [15], a treatment area in which herbalists have a long history of treatment [16-19]. Recently, elevated SUA has been

recognised as a marker of insulin resistance [20] and epidemiological studies indicate that a wide spectrum of disorders occur at levels of SUA that previously would have been considered benign [1]. In contrast to the dietary purines, the metabolism of fructose produces uric acid plus an additional array of toxins. Together these substances induce high levels of oxidative stress, NO depletion in the liver and proinflammatory effects on a wide range of tissues [5].

2. Uric Acid Metabolism

Uric acid is the final breakdown product of the metabolism of endogenous purine nucleotides (typically DNA, RNA and ATP) and exogenous food-derived purines [21]. Most mammals degrade uric acid to allantoin, via the hepatic enzyme uricase, and have SUA levels of 0.5 -2 mg/dL. In contrast, the uricase gene in the early hominoids turned non-functional, so today humans and the great apes have SUA levels exceeding those of other mammals [22, 23].

In the final phase of purine metabolism, the enzyme xanthine oxidase (XO) catalyses formation of uric acid, firstly from hypoxanthine and then xanthine. Pharmaceutical treatment of gout routinely involves the XO inhibitor therapy, with either allopurinol or febuxostat [24]. Hypoxanthine can then be reutilised by a salvage pathway involving the enzyme hypoxanthine-guanine phosphoribosyltransferese [25]. To what extent XO activity is influenced by diet and hormones is not fully elucidated but SUA levels do increase after menopause [26]. Also, glucose intake may affect both the production and excretion of uric acid by several mechanisms. An increased flux of glucose is thought to increase purine generation, while increased anaerobic glycolysis generates increased circulating lactate which leads to a reduction in renal excretion of uric acid [25].

Uric acid is a weak acid, with a pKa of 5.75, and almost all (98%) of the uric acid circulates in the serum as monosodium urate. Monosodium urate has a low solubility limit (6 mg/dl) and at higher concentrations (7 mg/dl) urate crystals precipitate in the synovial fluid [25]. Before the inflammation can occur, the urate crystals need to coated by serum proteins. After this a chain reaction occurs involving the NOD-like receptor P3 inflammasome, IL-1 and neutrophils [26]. It is thought that for gout to occur, the hyperuricemia must be associated with defects in the function of the genes regulating urate transport and homeostasis [26].

While monosodium urate is involved in multiple biological functions, including accounting for 60% of the total antioxidant capacity in the plasma [27], it can also be toxic and elevated SUA has long been regarded as the cause of gout and other joint diseases [15]. Urate is a powerful scavenger of reactive oxygen species and peroxynitrites [28] and stabilizes endothelial nitric oxide synthase (eNOS) activity. It chelates metals but cannot scavenge superoxide and only reaches its full plasma antioxidant capacity in the presence of ascorbic acid [28]. Uric acid may be involved in tissue healing activity by initiating inflammatory processes leading to the mobilisation of progenitor endothelial cells [26]. Inside the cell it exists in the soluble form, where paradoxically it has prooxidant and proinflammatory activities: oxidising lipids, reducing nitric oxide availability in endothelial cells and increasing reactive oxygen species [28]. It is suggested that it is elevated intracellular uric acid rather than extracellular that may be detrimental to health [29].

High levels of uric acid occur in the human cytosol, particularly in the liver, the endothelial cells and human nasal secretions [26] where uric acid plays a key role in respiratory defence [30]. Murine research indicates that uric acid also plays a key antioxidant role in the liver and that

treatment of elevated SUA, with the XO inhibitor allopurinol, reduces the hepatic total-radical trapping antioxidant parameter (TRAP) [31].

Reduced SUA has been linked to a variety of disease states, including multiple sclerosis, optic neuritis, Parkinson's disease, and Alzheimer's disease [32]. It is suggested that in these inflammatory neural diseases, the SUA is too low to prevent the toxicity from reactive oxygen and nitrogen species, particularly peroxynitrite [32]. Therapies are being researched to increase uric acid levels in the cerebrospinal fluid, for example using the uric acid precursor inosine [33].

Traditionally elevated SUA, referred to as hyperuricemia has been defined as > 7.0 mg/dl (450 µmol/l) for men and > 6.0 mg/dl (350 µmol/l) for women [20]. It has been suggested that elevated SUA could have provided an evolutionary advantage by acting to maintain blood pressure levels when salt intake levels were low. The elevated uric acid activates the renin angiotensin system reducing the excretion of sodium and increasing blood pressure but, when salt levels are high, such as in modern food, the uric acid contributes to hypertension [34]. It was noted as far back as the 1870s years that gout suffers had a high level of hypertension [35].

There are three sources of SUA:

1) Endogenous uric acid derives from the de novo synthesis and catabolism of nucleic acids. The production and catabolism of purines is approximately 300 - 400 mg daily [36]. This results in a daily production of endogenous uric acid estimated at 500 - 600 mg [15]. Uric acid is produced primarily in the liver, intestines, muscles, kidneys and the vascular endothelium [37]. Live and dying cells degrade their nucleic acids to uric acid [26].

2) The digestion/metabolism of purine compounds in foods produces urate in the intestine [21]. Purine compounds are the building blocks for DNA, RNA and ATP and are widely distributed throughout the plant and animal kingdoms. They are found in a high concentration in only a small number of foods and daily dietary uric acid is generally in the range 100 - 200 mg [15]. Thus, uric acid from purines is considerably less than endogenous production. It has been recommended to limit the intake of purines to 400 mg daily to avoid elevated SUA [4]. Choosing the traditional purine rich diet (Table 1) for 7-10 days can increase SUA of 1-2 mg/dl, while the low purine diet can lower SUA by an equivalent amount [20]. Purine compounds are found predominantly in meats, fishes and seafoods (Table 2-4).

Table 1 Traditional list of high and low purine containing foods [20].

High purine foods	**Low purine foods**
All meats, including organ meats and extracts	Dairy foods: milk, cheese, butter, eggs
Seafood	Grains/cereals: bread, pasta, cakes
Vegetables: peas, beans, lentils, aspagagus, spinach, mushrooms	Vegetables, fruits, nuts, except : peas beans, lentils, aspagagus, spinach
Yeast and yeast extracts	Sugar, sweets and gelatine
Beverages: beer and alcoholic drinks	Beverages: water, coffee, cocoa, tea, juices, carbonated beverages,

Table 2 Modern list of purine and uric acid levels in meats *[4] ^[38].

ANIMAL	CUT	Purine*	Uric acid*	Uric acid^	PS
BEEF	Entrecote	-	-	120	2
	Heart	185	224	554	3
	Kidney	174	203	269	3
	Liver	220	256	-	4
	Muscles	-	-	133	3
	Neck	101	121	-	3
	Rib loin	74	89	-	2
	Rump	-	-	120	2
	Shoulder ribs	77	93	120	2
	Shoulder sirloin	90	109	110	2
	Tenderloin	98	119	-	2
	Tongue	90	109	-	2
	Topside	111	135	110	3
VEAL	Fillet	-	-	140	2
	Kidney	-	-	218	3
	Muscles	-	-	172	3
	Neck – sweet bread	-	-	1260	5
	Shoulder	-	-	140	2
CHICKEN	Breast	141	172	175	3
	Buttocks	69	82	-	2
	Gizzard	143	170	-	3
	Heart	125	150	-	3
	Leg	123	150	110	3
	Liver	312	363	243	5
	Skin	120	143	-	3
	White meat	154	188	159	3
	Wing	138	168	-	3
DUCK		-	-	138	3
TURKEY		-	-	150	3
HORSE		113	137	200	3
LAMB/MUTTON		96	118	-	2
	Heart	-	-	241	4
	Muscles	-	-	182	3
PORK	Heart	119	145	530	3
	Kidney	195	232	334	3
	Liver	285	331	515	4
	Muscles	-	-	166	3
	Neck	71	86	-	2
	Ribs	76	93	-	2
	Rump	113	138	150	3
	Shoulder	81	99	150	2

	Shoulder, ribs	91	111	-	2
	Shoulder, sirloin	95	116	-	2
	Shoulder	108	131	-	3
	Sirloin	91	111	-	2
	Tenderloin	120	146	-	3
	Tongue	104	126	-	3
PROCESSED MEAT	Bacon	62	76	-	2
	Beef, corned	47	57	57	1
	Ham, boneless	74	91		2
	Ham, cooked	-	-	131	
	Ham, pressed	64	79	-	2
	Ham, Parma/Prosciutto	138	168	-	3
	Liver paste	80	94	-	2
	Liver sausage	-	-	165	3
	Salami	120	146	-	2
	Sausage, Frankfurt	50	61	89	1
	Sausage, Vienna	46	56	78	1

PS = purine score (1 <50 mg, 2 = 50 to 100 mg, 3 = 100 to 200 mg, 4 = 200 to 300 mg, 5 = >300 mg

Table 3 Modern list of purine and uric acid levels in fish and seafoods *[4] ^[38].

FOOD	TYPE	Purine*	Uric acid*	Uric acid^	PS
FISH	Amberjack, Japanese	121	148		3
	Anchovy, dried	1109	1314		5
	Anchovy, fresh			239	4
	Ayu	133	161		3
	Barracuda	148	180		3
	Bonito	211	259		4
	Carp	103	126	151	3
	Cod			109	2
	Eel	92	111	78	2
	Greenling, Arabesque	150	181		3
	Haddock			139	3
	Halibut, bastard	133	163	178	3
	Herring	140	170	210	3
	Mackeral, chub	122	150		3
	Mackerel, Jack	165	198	113	3
	Mackerel, Spanish	139	172	145	3
	Monkfish	70	84		2
	Monkfish, liver raw	104	122		3
	Pacific saury	155	185		3
	Plaice			93	2

	Red fish /Ocean perch			241	4
	Salmon	119	146	170	3
	Salmon, canned	133	160		3
	Sardine	210	247	345	4/5
	Seabass, Japanese	120	146		3
	Seabream	129	158		3
	Trout	181	217	297	3/4
	Tuna	157	193	178	3
	Tuna, canned	117	143	290	3/4
SEAFOOD	Caviar	95	111	144	2
	Clam	146	172		3
	Crab, king	100	119		2
	Crab, ovary	152	175		3
	Crab, snow	136	161		3
	Fish ball - processed	68	81		2
	Halibut roe			190	3
	Lobster	102	125	118	3
	Mussel			112	2
	Octopus	137	160		3
	Oyster	185	214	110	3
	Salmon roe	16	19		1
	Scallop	77	94	136	2
	Sea cucumber	6	7		1
	Sea urchin	137	161		3
	Shrimp	273	321	147	3/4
	Squid	161	190		3

PS = purine score (1 <50 mg, 2 = 50 to 100 mg, 3 = 100 to 200 mg, 4 = 200 to 300 mg, 5 = >300 mg

Table 4 Modern list of purine and uric acid levels in dairy, eggs, grains, nuts, beans and supplements *[4] ^[38].

CATEGORY	FOOD	Purine*	Uric acid*	Uric acid^	PS
DAIRY- cow	Cheese	6	7	7	1
	Milk	0	6	-	1
	Yogurt	0	6	8	1
EGG	Chicken egg	0	0	-	1
	Quail egg	0	0	-	1
GRAINS	Barley	44	52	94	1
	Buckwheat flour	76	89	-	2
	Millet			62	
	Oats	-	-	94	1
	Rice (polished)	26	30		1
	Rice (unpolished)	37	44		1
	Rice noodle	22	26		1

	Rye	-	-	51	1
	Wheat flour	16-26	18-30	51	1
NUTS	Almond	32	37	41	1
	Brazil nut	-	-	23	1
	Hazelnut			37	1
	Peanut	49	57	74	1
	Walnut	-	-	26	1
BEANS	Broad bean	36	42		1
	Green-peas -canned	19	22		1
	Soya bean - fermented	114	133		3
	Soya bean, green	48	56		1
	Soymilk	22	26		1
	Tofu, deep-fried	54	63		2
SUPPLEMENTS	Beer yeast	2996	3562	1810	5
	Chitin, Chitosan	1	1		1
	Chlorella	3183	3747		5
	DNA/RNA	21494	25641		5
	Glucosamine	12	14		1
	Polysaccharide	58	69		2
	Royal jelly	403	494		5
	Scales / collagen	3	3		1
	Soy isoflavone	7	8		1
	Spirulina	1077	1269		5

PS = purine score (1 <50 mg, 2 = 50 to 100 mg, 3 = 100 to 200 mg, 4 = 200 to 300 mg, 5 = >300 mg)

3) The metabolism of fructose by the liver yields glucose, lactate, glycogen and uric acid plus several toxins [39]. In nature, fructose may occur as a single molecule, i.e. a monosaccharide, or bound to a glucose molecule in the disaccharide sucrose [40]. Fructose is found in small amounts in vegetables (<3 g/100 g) (Table 5) and in varying amounts in fruits and fruit juices (1-35 g/100 g) (Table 6, Table 7) as the monosaccharide and within the sucrose molecule. Fructose is also found in honey (40 g/100g) as a monosaccharide and in the artificial sweeteners sucrose (50 g/100 g) and HFCS (45 or 55 g/100 g). These two artificial sweetens are used extensively in the manufacture of food products, both in the home and factory [14]. As noted above, in USA, even the lowest deciles of intakes in children, adolescents and teens, and adults, on average, exceed the recommendation for less than 10% of calories from added sugars, primarily from SSB [14] (Table 8). Studies determining a daily safe level of either fructose or added sugar have yet to be conducted, so the amounts that can safely ingested is unclear [39]. Furthermore, a systematic review reported that the current guidelines by various authorities, (for example the WHO Guideline: Sugars Intake for Adults and Children 2015), on dietary sugar do not meet criteria for trustworthy recommendations and are based on low-quality evidence [41].

Additionally, exposure to lead can increase SUA [42].

Table 5 Fructose, glucose and sucrose levels and purine levels in vegetables g per 100 g *[43] ^[38].

Vegetable - raw	FRU*	GLU*	SUC*	TF*	FRU^	GLU^	SUC^	TF^	PU^	FS	PS
Alfalfa seeds, sprouted	0.1	0.1	0.0	0.1	-	-	-	-	-	1	-
Artichokes, boiled	0.0	0.2	0.7	0.4	1.7	0.8	0.1	1.8	78	1	1
Asparagus	1.0	0.7	0.2	1.1	1.0	0.8	0.2	1.1	23	1	1
Aubergine /Egg plant	1.5	1.6	0.3	1.7	1	1	0.2	1.1	21	1	1
Bamboo shoots	-	-	-	-	0.4	0.4	0.2	0.5	29	1	1
Beans, haricot	1.4	1.5	0.4	1.6	1.3	1.0	0.4	1.5	37	1	1
Beetroot	0.2	0.3	5.3	2.8	0.3	0.3	7.9	4.3	19	1	1
Broccoli	0.7	0.5	0.1	0.7	1.1	1.1	0.5	1.4	81	1	1
Brussels sprouts	0.9	0.8	0.5	1.2	0.8	0.9	1.1	1.4	69	1	1
Cabbage	1.5	1.7	0.1	1.5	1.8	2.0	0.3	2.0	22	1	1
Carrots	0.6	0.6	3.6	2.3	1.3	1.4	2.1	2.4	17	1	1
Cauliflower	1.0	0.9	0.0	1.0	0.9	0.9	0.2	1.0	51	1	1
Celery, stalks	0.4	0.4	0.1	0.4	0.1	0.0	2.1	1.2	-	1	-
Celery, root	-	-	-	-	0.1	0	1.7	1.0	30	1	1
Corn, sweet, yellow	1.9	3.4	0.9	2.4	0.4	0.6	2.1	1.5	52	1	1
Cucumber	0.8	0.6	0.0	0.8	0.9	0.9	0.1	1.0	7	1	1
Kale	0.4	0.4	0.2	0.5	0.9	0.6	1.0	1.4	48	1	1
Kohirabi	-	-	-	-	1.4	1.2	1.1	2.0	25	1	1
Leek	-	-	-	-	1.2	1	0.8	1.6	74	1	1
Lettuce, green leaf	0.4	0.4	0.0	0.4	0.5	0.4	1.0	1.0	13	1	1
Lima beans, cooked	0.2	0.0	1.1	0.8	-	-	-	-	-	1	-
Mushrooms	0.0	1.2	0.0	0.0	0.2	0.2	0.1	0.3	58	1	1
Okra	0.6	0.3	0.6	0.9	0.8	0.7	0.2	0.9	-	1	-
Onions, green tops	2.1	1.6	0.2	2.2	0.8	0.7	0.7	1.2	67	1	1
Onions	1.3	2.0	1.0	1.8	1.4	1.6	1.9	2.4	13	1	1
Onions, sweet	2.0	2.3	0.7	2.4	0.8	0.7	0.2	0.9	67	1	1
Parsley, leaf	-	-	-	-	0.3	0.5	na	0.3	-	1	-
Parsley, root	-	-	-	-	0.7	0.6	4.8	3.1	-	2	-
Parsnip	-	-	-	-	0.3	0.2	2.6	1.6	-	1	-
Peas, green	0.4	0.1	5.0	2.9	0.1	0.1	1.2	0.7	84	1	1
Peppers, jalapeno	2.6	1.5	0.0	2.6	-	-	-	-	-	1	-
Peppers, green	1.1	1.2	0.1	1.2	1.3	1.4	0	1.3	55	1	1
Peppers, red	2.3	1.9	0.0	2.3	-	-	-	-	-	1	-
Potatoes	0.3	0.4	0.4	0.5	0.2	0.2	0.3	0.4	16	1	1
Pumpkin	-	-	-	-	1.1	1.0	0.1	1.2	44	1	1
Radishes	0.7	1.1	0.1	0.8	0.7	1.2	0.2	0.8	15	1	1
Rutabagas	1.6	2.3	0.5	1.9	0.7	0.3	0.0	0.7	-	1	-
Spinach	0.2	0.1	0.1	0.2	0.1	0.1	0.2	0.2	57	1	1
Squash, summer	1.0	0.8	0.0	1.0	1.1	1.0	0.1	1.2	44	1	1
Squash, winter	0.0	1.0	0.2	0.1	1.4	1.4	1.8	2.3	-	1	-
Tomatoes	1.4	1.3	0.0	1.4	1.4	1.1	0.0	1.4	11	1	1

Turnip greens	0.3	0.5	0.0	0.3	-	-	-	-	-	1	-
Turnip	-	-	-	-	1.5	1.9	0.5	1.8	-	1	1
Tomatoes, red	1.4	1.3	0.0	1.4	1.4	1.1	0.0	1.4	11	1	-

FRU = fructose, GLU = glucose, SUC = sucrose, TF = total fructose, Purines expressed as uric acid/100 g, FS = Fructose score (1 <3 g, 2 = 3 to 4.5 g, 3 = 4.5 to 6.0 g, 4 = 6.0 to 7.5 g, 5 = 7.5 to 9.0 g, 6 >9 g), PS = purine score (1 <50 mg, 2 = 50 to 100 mg, 3 = 100 to 200 mg, 4 = 200 to 300 mg, 5 = >300 mg).

Table 6 Fructose, glucose and sucrose levels and purine levels in fruit g per 100 g *[43] ^[38].

FRUIT	FRU*	GLU*	SUC*	TF*	FRU^	GLU^	SUC^	TF^	PU^	FS	PS
Apples	5.9	2.7	1.9	**6.8**	5.7	2.0	2.5	**7.0**	14	4	1
Apricots	0.9	2.4	5.9	**3.9**	1.7	0.9	5.1	**4.3**	-	2	-
Apricots, dried	12.5	33.1	7.9	**16.4**	4.9	9.7	29.0	**19.4**	73	6	1
Avocados	0.1	0.4	0.1	**0.2**	0.2	0.1	0.1	**0.3**	19	1	1
Bananas	4.9	5.0	2.4	**6.0**	3.4	3.5	0.0	**3.4**	57	4	1
Bilberry	3.7	3.3	0.0	**3.7**	3.3	2.5	0.2	**3.4**	22	2	1
Blackberries	2.4	2.3	0.1	**2.4**	3.1	2.2	0.0	**3.1**	-	1	-
Blueberries	5.0	4.9	0.1	**5.0**	-	-	-	-	-	3	-
Cherimoya	6.3	5.9	0.7	**6.6**	-	-	-	-	-	4	-
Cherries, Morello	-	-	-	-	5.2	4.3	0.4	**5.4**	17	3	1
Cherries, sour	3.5	4.2	0.8	**3.9**	-	-	-	-	-	2	-
Cherries, sweet	5.4	6.6	0.2	**5.4**	6.3	7.1	0.2	**6.4**	17	3	1
Clementines	1.6	1.6	6.0	**4.6**	-	-	-	-	-	3	-
Cranberries	0.7	3.4	0.2	**0.8**	2.9	3.0	0.1	**3.0**	na	1	-
Currants, red/black	3.5	3.2	0.6	**3.8**	2.8	2.8	0.3	**3.9**	17	2	1
Dates, deglet noor	19.6	19.9	23.8	**31.5**	-	-	-	-	-	6	-
Dates, medjool	32.0	33.7	0.5	**32.2**	-	-	-	-	-	6	-
Date, dried	-	-	-	-	25	25	14	**32.0**	34	6	1
Feijoa	3.0	2.3	2.9	**4.4**	-	-	-	-	-	2	-
Figs, dried	22.9	24.8	0.1	**23.0**	24.0	26.0	6.0	**27.0**	84	6	1
Grapefruit	1.8	1.6	3.5	**3.5**	2.1	2.3	2.9	**3.6**	-	2	-
Grapes, muscadine	3.9	3.7	0.6	**4.2**	-	-	-	-	-	2	-
Grapes	8.1	7.2	0.2	**8.2**	7.1	7.1	0.4	**7.3**	27	5	1
Grapes, dried	32.5	29.8	0.0	**32.5**	33.0	32.0	1.9	**34.0**	107	6	2
Guava	-	-	-	-	3.4	2.1	0.3	**3.6**	-	2	-
Jackfruit	9.2	9.5	0.4	**9.4**	1.7	6.0	6.9	**5.2**	-	5	-
Kiwifruit, green	4.4	4.1	0.2	**4.4**	4.6	4.3	0.2	**4.7**	19	2	1
Kiwifruit, gold	5.8	5.3	1.2	**6.4**	-	-	-	-	-	4	-
Lemons	1.1	1.0	0.4	**1.3**	1.4	1.4	0.4	**1.6**	-	1	-
Limes	0.6	0.6	0.5	**0.9**	0.8	0.8	0.3	**1.0**	-	1	-
Mandarin	2.4	2.1	6.1	**5.4**	1.3	1.7	7.1	**4.9**	-	3	-
Mangos	4.7	2.0	7.0	**8.2**	2.5	0.9	9.0	**7.0**	-	5	-
Melons	1.9	1.5	4.4	**4.0**	1.3	1.8	9.5	**6.1**	-	2	-

Nectarines	1.4	1.6	4.9	**3.8**	-	-	-	-	-	2	-
Oranges	2.3	2.0	4.3	**4.4**	2.5	2.3	3.4	**4.2**	19	2	1
Papayas	3.7	4.1	0.0	**3.7**	3.5	3.6	0.0	**3.5**	-	2	-
Peaches	1.5	2.0	4.8	**3.9**	1.2	1.0	5.7	**4.1**	21	2	1
Pears	6.4	2.6	0.7	**6.8**	6.7	1.7	1.8	**7.6**	12	4	1
Persimmons	5.6	5.4	1.5	**6.3**	8.0	7.0	1.0	**8.5**	-	4	-
Pineapple	2.1	1.7	6.0	**5.1**	2.4	2.1	7.8	**6.3**	19	3	1
Plantains, green	1.0	1.1	0.2	**1.1**	0.2	0.7	0.1	**0.3**	-	1	-
Plums, raw	3.1	5.1	1.6	**3.9**	2.0	3.4	3.4	**3.7**	24	2	1
Plums, dried (prunes)	12.5	25.5	0.2	**12.5**	9.4	0.0	0.0	**9.4**	64	6	1
Pomegranate	-	-	-	-	7.9	7.2	1	**8.4**	-	5	-
Raspberries	2.4	1.9	0.2	**2.5**	2.1	1.8	1.0	**2.6**	18	1	1
Strawberries	2.4	2.0	0.5	**2.7**	2.2	2.2	1.0	**2.7**	21	1	1
Watermelon	3.4	1.6	1.2	**4.0**	3.9	2.0	2.4	**5.1**	-	2	-

FRU = fructose, GLU = glucose, SUC = sucrose, TF = total fructose, Purines expressed as uric acid/100 g, FS = Fructose score (1 <3 g, 2 = 3 to 4.5 g, 3 = 4.5 to 6.0 g, 4 = 6.0 to 7.5 g, 5 = 7.5 to 9.0 g, 6 >9 g), PS = purine score (1 <50 mg, 2 = 50 to 100 mg, 3 = 100 to 200 mg, 4 = 200 to 300 mg, 5 = >300 mg.

Table 7 Fructose, glucose and sucrose levels in fruit juices g per 100 g *[43] ^[38].

FRUIT	**FRU***	**GLU***	**SUC***	**TF***	**FRU^**	**GLU^**	**SUC^**	**TF^**	**FS**
Apple juice	5.7	2.6	1.3	**6.4**	6.4	2.4	1.7	**7.3**	4
Apricot nectar	4.5	4.2	4.1	**6.5**	-	-	-	**-**	4
Cherry juice, Morello	-	-	-	**-**	5.3	6.5	0.0	**5.3**	3
Coconut water	2.1	0.8	1.0	2.6	-	-	-	**-**	**1**
Grape juice	7.4	6.8	0.0	**7.4**	8.3	8.1	0.2	**8.4**	5
Grapefruit juice	2.8	2.7	2.5	**4.0**	4.2	4.3	1.6	**5.0**	2
Lemon juice	1.1	1.0	0.4	**1.3**	1.0	1.0	0.4	**1.2**	1
Lime juice	0.6	0.6	0.5	**0.9**	-	-	-	**-**	1
Mandarin	2.4	2.1	6.1	**5.4**	3	1.6	5	**5.5**	4
Mango nectar	5.6	5.3	1.0	**6.1**	-	-	-	**-**	4
Orange juice	2.4	2.3	4.1	**4.5**	2.3	2.2	4.1	**4.4**	3
Peach nectar	5.4	5.2	0.6	**5.7**	-	-	-	**-**	3
Pineapple juice	3.8	4.7	1.5	**4.6**	2.6	2.6	4.5	**4.9**	3
Pomegranate juice	6.4	6.3	0.0	**6.4**	-	-	-	**-**	4
Raspberry juice	-	-	-	**-**	3.1	2.4	0	**3.1**	3

FRU = fructose, GLU = glucose, SUC = sucrose, TF = total fructose, Purines expressed as uric acid/100 g, FS = Fructose score (1 <3 g, 2 = 3 to 4.5 g, 3 = 4.5 to 6.0 g, 4 = 6.0 to 7.5 g, 5 = 7.5 to 9.0 g, 6 >9 g).

Table 8 Fructose, glucose and sucrose levels in prepared beverages g per 100 g [1][44], [2][43], [3][45].

Beverage	FRU[1]	GLU[1]	SUC[1]	TF	FRU[2]	GLU[2]	SUC[2]	TF	FRU[3]	GLU[3]	SUC[3]	TF	FS
Sierra Mist Natural	0.7	0.6	8.7	**5.1**	-	-	-	-	-	-	-	-	3
Gatorade Lemon-Lime	2.3	2.5	0.9	**2.8**	-	-	-	-	2.1	2.4	1.4	**2.8**	1
Ginger Ale	4.5	5.1	0.0	**4.5**	3.7	3.1	1.9	**4.7**	-	-	-	-	3
Pepsi Throwback	4.2	4.0	3.0	**5.7**	-	-	-	-	-	-	-	-	3
7-Up	4.6	3.1	0.0	**4.6**	-	-	-	-	-	-	-	-	3
Coca-Cola - Mexican	5.1	4.8	1.2	**5.7**	-	-	-	-	5.4	5.0	0.0	**5.4**	3
Cola	5.3	5.9	0.0	**5.3**	5.8	4.1	0.0	**5.8**	-	-	-	-	3
Arizona Iced Tea	5.9	4.0	0.0	**5.9**				**0.0**	5.9	4.3	0.0	**5.9**	3
Dr.Peppar	6.1	4.0	0.0	**6.1**				**0.0**	5.9	4.1	0.0		4
Coca-Cola	6.3	4.2	0.0	**6.3**				**0.0**	7.2	3.9	0.0	**7.2**	4
Sprite	6.3	4.1	0.0	**6.3**	5.2	3.1	0.7	**5.5**	6.6	3.7	0.0	**6.6**	4
Pepsi	6.6	4.4	0.0	**6.6**	-	-	-	-	7.4	3.9	0.0	**7.4**	4
Mug Root Beer	6.7	4.6	0.0	**6.7**	-	-	-	-	-	-	-	-	4
Mountain Dew	7.2	4.8	0.0	**7.2**	-	-	-	-	7.0	5.0	0.0	**7.0**	4
Energy drink, ROCKSTAR	-	-	-	-	3.6	6.0	2.7	**4.9**	-	-	-	-	3
Energy drink, Monster	-	-	-	-	2.4	4.1	4.4	**4.6**	-	-	-	-	3
Energy drink, RED BULL	-	-	-	-	1.6	3.4	5.2	**4.2**	1.9	3.6	5.1	**4.5**	3
Snapple - Kiwi Strawberry	-	-	-	-	-	-	-	-	4.9	4.8	1.2	**5.5**	3
Vitamin Water	-	-	-	-	-	-	-	-	4.0	0.7	0.7	**4.4**	2
Tea, black, ready-to-drink	-	-	-	-	4.8	3.6	1.1	**5.3**	-	-	-	-	3
Wine - dessert, sweet	5.15	2.6	0.05	**5.2**	-	-	-	-	-	-	-	-	3
Wine, rose	2.1	1.7	0	**2.1**	-	-	-	-	-	-	-	-	1
Wine, dessert, dry	0.47	0.58	0	**0.5**	-	-	-	-	-	-	-	-	1
Beer, regular, all	--	--	0	**0.0**	-	-	-	-	-	-	-	-	1
Tea, green, brewed	--	--	0	**0.0**	-	-	-	-	-	-	-	-	1

Coffee, brewed	--	--	0	**0.0**	-	-	-	-	-	-	-	-	1

FRU = fructose, GLU = glucose, SUC = sucrose, TF = total fructose, FS = Fructose score (1 = <3 g, 2 = 3 to 4.5 g, 3 = 4.5 to 6.0 g, 4 = 6.0 to 7.5 g, 5 = 7.5 to 9.0 g, 6 = >9 g).

Uric acid is partly excreted in the urine, 400 – 600 mg daily, and partly via the intestines, 300 mg daily [4], although other sources state that the kidneys excrete 70% of the uric acid total [35]. It is thought that SUA is tightly controlled, by balancing the production of uric acid from purine nucleosides by the liver (XO activity) and the uric acid excretion into urine [46].

The traditional pathophysiological model of uricemia involved only two mechanisms:

A. Overproduction type due to upregulated activity of XO; and
B. Renal underexcretion type.

As less than 10% of hyperuricaemia results from overproduction, the primarily cause of hyperuricaemia has widely regarded as reduced renal excretion [20, 47].

Recently a three-mechanism model, including intestinal secretion, has been proposed:

A. Renal overload type:

A1. Overproduction type due to upregulated activity of XO; and

A2. Extra-renal / Intestinal underexcretion type (mostly ABCG2 dysfunction); and

B. Renal underexcretion type [36].

The urinary excretion of uric acid is complicated as it involves both secretion and reabsorption at multiple points in the proximal tubule. In healthy adults, the normal urinary urate excretion is in the range of 250 - 750 mg daily, yet the fractional urate excretion is only 8% to 10% [35]. In the proximal tubular cells secretory transporters occur at the basal membrane: OAT1, OAT2 and OAT3; and at the apical membranes: ABCG2 or BCRP, NPT1 NPT4 and MRP4; while reabsorption transporters URAT1 and URATv1 occur at both the apical and basolateral membranes. Genetic polymorphisms of BCRP, NPT1 and NPT4 transporters are associated with gout and/or hyperuricemia [46]. Uricosuric drugs inhibit URAT1, hindering reabsorption and increasing the excretion of uric acid [25]. Elevated levels of the hormones insulin, adrenaline and parathyroid hormone all reduce renal excretion of uric acid [25].

Decreasing urinary pH levels, both decrease renal clearance of uric acid and stimulate nephrolithiasis, which further negatively affects kidney function [48]. At urinary levels < pH 5.5, uric acid crystallisation and stone formation occurs. The main causes of low pH are elevated SUA, high levels of uric acid excretion, chronic diarrhea, severe dehydration and diabetic ketoacidosis [26]. Individuals with gout have the double the risk of developing kidney stones [49] while gout is independently associated with both chronic kidney disease and nephrolithiasis [50]. Kidney stones are associated with several aspects of the metabolic syndrome: type 2 diabetes mellitus, obesity and hypertension [51]. In USA, the prevalence of kidney stones amongst men is 10.6% and women 7.1% [52].

Virtually all uric acid produced in the liver enters the systemic blood circulation. Consequently, bile contains only small amounts uric acid and does not play a significant role in excretion. Rather, intestinal or “extra-renal” elimination involves the absorption of uric acid, from the circulation, by the intestinal epithelial cells [46]. The excretion of uric acid occurs in the digestive juices secreted in the upper small intestine, primarily the duodenum, with uric acid concentrations of 0.2 mg/ml having been reported in mice [53]. Limited uric acid excretion may also occur via the jejunum, the

ileum and the colon [46]. As humans produce between one and two litres intestinal digestive secretions per day [54, 55], the efficiency of these intestinal secretions in removing uric acid is clinically relevant. The uric acid secreted into the intestines appears to be completely degraded by uricolytic bacteria to waste substances, except in cases of dysbiosis where uric acid is excreted in faeces [56]. Exogeneous urate, resulting from the digestion of purines, may be either absorbed by the intestine or degraded in the intestine but normally, it is not found in the faeces [21]. The secretory transporter in the intestine is ABCG2 [36], whose genetic polymorphisms are associated with gout and/or hyperuricemia. Thus, the ABCG2 transporter plays an important role in both the urinary secretion and intestinal secretion of uric acid. In cases of ABCG2 dysfunction, the intestinal excretion of uric acid decreases whereas, urinary excretion of uric acid increases as the kidneys seek to regulate SUA [36]. In a group of hyperuricemia patients, 75% exhibited ABCG2 dysfunction [36] demonstrating the importance of intestinal secretion in diagnosing and treating hyperuricaemia. With regard to intestinal secretion of uric acid, even a single dose of fructose has been shown, in rats, to decrease intestinal excretion of uric acid [57].

Some diets and medicines influence both SUA and uric acid excretion:

- SUA increases in situations when ketosis occurs, such as a high-fat diets, starvation and fasting [25];
- salt restriction (<2 g/day) increases SUA by 1.8 to 2.0 mg/dl [25];
- vitamin B3 (niacin) therapy for elevated cholesterol levels may increase SUA [25];
- alcohol intoxication elevates lactate and which inhibits renal urate excretion [25];
- osteoporosis therapy with Teriparatide increased SUA [58];
- amongst cardiovascular antihypertensives, the longitudinal change in serum urate levels was 0.72 mg/dl (95% CI 0.57, 0.87) higher in those who began treatment with a diuretic than in those who did not ($P < 0.001$) [59];
- antibiotic usage increases the incidence of kidney stones, particularly among young children [60] and thus affects their ability to excrete uric acid. The possibility that antibiotics may disturb the microbiota, alter intestinal excretion and contribute to metabolic syndrome is supported by animal research [61].

An excess of SUA is referred to as hyperuricemia and is variably defined as a serum urate level greater than either 6.8 mg/dl [21], 7.0 mg/dl [24] or 7.2 mg/dl [47]. As SUA increases so does the intracellular urate and, in hyperuricemia, crystals of monosodium urate precipitate in the synovial joints and periarticular tissues. Other tissues may also be affected such as the tendons, kidneys, heart valves and pericardium [26]. For symptoms to occur, the crystals need to be coated by serum proteins. Only then can a chain reaction start, involving the NOD-like receptor P3 inflammasome, IL-1 and neutrophils. It is thought that for gout to occur, hyperuricemia must be associated with defects in the genes regulating urate transport and homeostasis [26]. It has been recommended that gout suffers maintain a SUA <6 mg/dl, both to relieve symptoms and to deplete urate crystal concentrations. Severe suffers should aim for a SUA <5 mg/dl [24]. Still, not everyone with hyperuricemia develops gout and the inflammation process involved is complex and not fully understood [26]. It has long been known that both insulin resistance and SUA concentrations are inversely related to urinary uric acid clearance [62]. Clinical studies report that a reduction of SUA, following treatment with either XO inhibitors or renal stimulants, improves insulin sensitivity [63].

Elevated SUA has for many years been clinically associated with gout, so much so, that in situations when the symptoms of gout were controlled, there has been only limited clinical interest in SUA levels [47]. This is despite the observation, as far back as the 1870s, that gout suffers had a high level of hypertension [35]. Since the discovery of the important functions of nitrous oxide (NO), it has been suspected that hyperuricemia inhibits NO synthase and that decreased NO might be a mechanism leading to insulin resistance [64].

In recent times there has been a continuous stream of publications indicating that elevated SUA has health implications. Hyperuricemia has been reported to be

- 1998: a strong predictor of stroke [65];
- 2004: a marker of all-cause mortality [66]
- 2006: a strong risk factor for myocardial infarction and stroke [67];
- 2008: a strong and independent risk factor for Type II diabetes [68];
- 2009: an independent risk factor of mortality from all causes, total CVD, and ischemic stroke in the Taiwanese general population in high-risk groups, and potentially in low-risk groups [69];
- 2012: an independent risk factor for metabolic syndrome [70];
- 2013: a predictor of future metabolic syndrome [71];
- 2014: the most reliable predictor for the development of hypertension [35];
- 2014: the major predictor for the development of incident kidney disease [35];
- 2015: a significant and independent measure associated with increased risk of stroke recurrence in ischemic stroke patients [72];
- 2015: an increased risk predictor of metabolic syndrome regardless of the study characteristics [73];
- 2015: a significant factor in the prevalence and development of Non-alcoholic Fatty Liver Disease [73];
- 2016: independently associated with the occurrence of atrial fibrillation [74];
- 2017: an independent cardiovascular risk factor, as manifested by increased carotid intima-media thickness in rheumatoid arthritis patients [75];
- 2018: associated with increased risk of heart failure in older men on antihypertensive treatment [76];
- 2018: the most adverse risk profile for heart failure including underlying ischemia for treated hypertensive men [76];

Fifteen years ago, it was suggested that mild hyperuricemia may have a pathogenic role in the development of cardiovascular and renal diseases [22]. Shortly later, it was hypothesised that fructose-induced hyperuricemia was a causal mechanism for the epidemic of the metabolic syndrome [77]. Some researchers are now claiming that that SUA, at levels not sufficiently high to produce the symptoms of gout, is a contributory causal factor for the metabolic syndrome, hypertension, diabetes, Non-alcoholic Fatty Liver Disease and chronic kidney disease [29]. These disorders have grouped under the name “cardio-nephro-metabolic” disorders and it has been proposed that an appropriate threshold level for SUA is 6 mg/dl for both men and women [47].

Yet, even this value may be too high, according to a study from Iran, where metabolic syndrome is highly prevalent at 30%. SUA and metabolic syndrome measurements were conducted in a group of untreated participants, where individuals with a history of cardiovascular disease, diabetes, cancer, stroke, kidney disease and gout were excluded. Those classified with

metabolic syndrome had a mean SUA of 5.9 ± 1.5 mg/dl while the other participants had a mean SUA of 4.9 ± 1.3 mg/dl [78]. This study suggests that a more appropriate threshold for SUA may be 5 mg/dl or less.

Can SUA be too low? It has been reported that, both low (<3.5 mg/dl for men and <2.5 mg/dl for women) and high (≥9.5 mg/dl for men and ≥8.5 mg/dl for women) SUA levels are associated with increased all-cause, cardiovascular disease, and cancer mortality [79]. Yet, another study, of the elderly, reported that while low levels of SUA (< 4.0 mg/dl) were associated with degenerative neural conditions, this occurred only in the undernourished [80]. Smokers with a lower SUA were reported to suffer more respiratory disease than average SUA smokers. However, average weight in the lowest SUA quintile was only 69 kg, compared to the average weight for the study of 80 kg [81], so the nutritional status of the lowest SUA quintile in this study is open to question. Similarly, in a study of 45 Type 1 diabetics, ranging in age from 18 to 65 years, the fasting mean SUA value was 4.1 ± 0.9 mg/dl [82]. This low SUA value may reflect undernourishment in almost 50% of the study group, Additionally, it is possible that the low SUA indicates either a loss of kidney function or an early stage of chronic kidney disease [83]. So, given our current state of knowledge we can assume that low SUA levels are not a major problem except in the undernourished.

3. One Disaccharide and Two Monosaccharides

Sucrose, common table sugar, is a disaccharide composed of two monosaccharides, fructose and glucose. Small amounts of sucrose occur naturally in the roots and fruits of plants, but commercial sources of sucrose are derived from sugar cane and sugar beets [84]. The bonding between fructose and glucose is relatively strong, so sucrose does not readily hydrolyse in water. During digestion the intestinal digestive enzyme, sucrase, splits the sucrose molecule into fructose and glucose [84]. When deriving total fructose intake measures in foods, it is important to combine free fructose values and add 50% of the sucrose value to account for the fructose segment of the sucrose.

Sugar intake in developed countries has increased dramatically over the last century, while in the last 50 years, similar increases have occurred in the developing countries. As half of sucrose is fructose and the other half is glucose, epidemiological studies cannot distinguish between glucose and fructose intake. Developed countries consume 40 to 50 kg sucrose per person per annum, while some countries in Central America and South America exceed this intake, for example Brazil at 67 kg per person per annum [85].

Glucose is the most abundant monosaccharide in carbohydrate foods, as well as, occurring in both soluble and insoluble dietary fibres. Vegetable starches and animal glycogen (primarily from liver) are made exclusively of glucose. In starchy foods, glucose is found primarily in polymer forms, such as amylose and amylopectin. These two starches provide over half of the food energy in the USA [84]. Digestive enzymes from saliva and the pancreas cleave glucose-glucose bonds. Glucose is actively taken up by the small intestine. A small amount of glucose is used by the enterocytes, but most enters the portal vein where it dissolves into the plasma in free form. Elevated blood glucose levels stimulate the release of insulin. Glucose is used throughout the body by cells as an energy source, with the rate of entry into cells accelerated by insulin. Excess glucose is stored in the liver and muscles, and only a little glucose is lost through the urine. Stored glycogen is released as needed to control blood glucose levels [84].

Fructose is absorbed into the jejunum enterocytes and then transported to the liver via the portal vein [5]. It is extensively metabolised by the liver with only very small amounts entering the systemic blood circulation. Fructose is not essential, although involved in a number of body processes, as needs can be meet by endogenous production from glucose [84]. Fructose occurs naturally in fruits (1-35 g/100g), some vegetables (<3 g/100g) and honey (40 g/100g). The fructose content increases in fruits and vegetables as they ripen (Table 8). Fructose also occurs in equal amounts to glucose in sugar and HFCS. In sucrose, the fructose and glucose are completely bonded whereas in HFCS they are in the free form [6].

HFCS, a sweetener used extensively used in USA , is derived from corn starch [3]. Corn starch, a chain of glucose molecules, is broken down to individual molecules to produce corn syrup [6]. Enzymes, added to corn syrup, convert approximately half of the glucose molecules to fructose molecules. HFCS 42 contains 42% fructose while HFCS 55 contains 55% fructose, the remainder is water and glucose. HFCS 42 is used in the production of processed foods while HFCS 55 is used in the production SSBs. Notably, the proportion of fructose to glucose in both HFCS types are similar to that of sucrose [6]. The principal difference between the two is that in HFCS, fructose and glucose are unbonded so that no enzymic activity is required for their intestinal absorption, whereas in sucrose the two monosaccharides need to be split before intestinal absorption occurs.

Although fructose has the same chemical formula as glucose, $C_6H_{12}O_6$, they are structurally different and are metabolised differently. Whereas glucose passes into the general circulation, fructose is almost completely absorbed and metabolised by the liver. Fructose metabolism occurs independently of insulin, which explains why it has a low glycaemic index. In the liver fructose is phosphorylated into fructose 1-phosphate in a reaction catalysed by fructokinase. This reaction is rapid and without negative feedback, and hugely decreases the levels of intracellular phosphate and ATP. Next, the enzyme fructose-1-p aldolase breaks fructose 1-phosphate into dihydroxyacetone phosphate and D-glyceraldehyde. When there is a high intake of fructose, phosphorylation into fructose 1-phosphate is fast, but the reaction with aldolase is slow. The accumulation of fructose 1-phosphate and the reduction of intracellular phosphate stimulates AMP deaminase, which catalyses the degradation of AMP to inosine monophosphate, increasing the rate of purine degradation. The purine degradation produces uric acid as well as generating mitochondrial oxidants. Mitochondrial oxidative stress then induces aconitase inhibition in the Krebs cycle, with accumulation of citrate and stimulation of ATP citrate lyase and fatty acid synthase. The result is de novo lipogenesis and hepatic fat accumulation. The increase in intracellular uric acid is followed by an acute rise in circulating levels of SUA, which is likely due to uric acid release from the liver. Additionally, fructose stimulates uric acid synthesis from amino acid precursors such as glycine. Long-term fructose administration suppresses renal excretion of uric acid, resulting in elevated SUA [1]. Other research reports that even high fructose intake for less than a week inhibits urinary uric acid excretion [86].

The primary metabolites of fructose are glucose (50%), lactate (25%), glycogen (15%), uric acid, methylglyoxal, ceramide, triglyceride and free fatty acids [39]. Elevated levels of these fructose metabolites may induce insulin resistance, as well as, causing an overproduction of reactive oxygen species, leading to the secretion of inflammatory cytokines and the disruption of tissue function (Table 9). Fructose and its metabolites directly and/or indirectly cause oxidative stress, chronic inflammation, endothelial dysfunction, lipid accumulation, autophagy, increased intestinal permeability and aggravate the metabolic syndrome with tissue and organ dysfunctions [5].

Furthermore, the intake of fructose is likely to worsen inflammatory conditions, regardless of cause.

Table 9 Impact of fructose metabolites on organ function [5].

Organs	**Factors**	**Pathological Indexes**	
Histopathological Changes		**Increase**	**Decrease**
Adipose tissue	FFA	ROS production	Insulin sensitivity
Inflammation response	UA	Inflammatory cytokine flux	Leptin sensitivity
Endothelial dysfunction		FFA uptake	Glucose uptake
		Adiponectin secretion	Oxygen availability
		Lipid accumulation	
		Autophagy	
Brain	FFA	ROS production	Insulin sensitivity
Appetite increase	UA	Inflammation cytokine flux	Leptin sensitivity
Psychological stress	MG	Food intake	
Heart/vessel	FFA	ROS production	Insulin sensitivity
Hypertrophy	UA	FFA uptake	Glucose
Endothelial dysfunction		Vascular tone	consumption
Plaque formation		RAGE production	Vascular
Vascular stiffness		Blood pressure	vasodilation
		Insulin sensitivity	
		Glucose consumption	
		Vascular vasodilation	
Intestine	UA	Endotoxin translocation	Insulin sensitivity
Increased intestinal		Bacterial composition	
permeability		disturbance	
		Dysregulation of tight	
		junction protein	
Kidney	UA	ROS production	Insulin sensitivity
CKD	MG	Inflammatory cytokine flux	UA clearance
Endothelial dysfunction		Dysregulation of renal	
		organic ion	
		transporters	
		NO production	
		Urine sodium retention	
Liver	Lactate	Gluconeogenesis	Insulin sensitivity
Steatosis	FFA	Glucose export	Glucose
NAFLD	DAG	ROS production	consumption
Fibrogenesis	Ceramide	De novo lipogenesis	Glucose uptake
Endothelial dysfunction	UA	Inflammatory cytokine flux	Oxygen availability

	MG	Lipid accumulation Mitochondrial dysfunction VLDL-secretion	
Pancreatic islet Glucose intolerance Increased cell mass Irregular insulin secretion	Glucose FFA UA	Inflammatory cytokines flux ER stress Apoptosis	Insulin sensitivity Leptin sensitivity
Skeletal muscle Inflammation response Endothelial dysfunction	Lactate FFA Ceramide UA	FFA uptake Autophagy Inflammatory cytokine flux Lipid accumulation	Insulin sensitivity Glucose uptake Oxygen availability

DAG: diacylglycerol; FFA: free fatty acid; MG: methylglyoxal; UA: uric acid.

As well as the oxidative stress produced by the metabolism of fructose, the fructose metabolite uric acid decreases NO bioavailability by multiple mechanisms and increases cardiovascular risk [87]. Intracellular uric acid has been suggested as the cause of both insulin resistance and enhanced gluconeogenesis by stimulating the NADPH enzyme to cause oxidative stress, mitochondrial injury and ATP depletion [63].

High dietary levels of fructose appear to have a greater physiological impact than glucose. When two groups of overweight adults, consumed 25% of their energy requirements, for 10 weeks, either as glucose- or fructose-sweetened beverages, only the fructose consumers experienced increased hepatic de novo lipogenesis, dyslipidaemia, and visceral adiposity, and decreased insulin sensitivity [7]. In a follow-up study with a similar design, it was reported that fructose, but not glucose, increased circulating uric acid, increased gamma-glutamyl transferase activity (suggesting altered hepatic function) and increased the production of retinol binding protein-4 (linked to visceral adiposity) [8].

It has been argued that, “sucrose, HFCS, invert sugar, honey, and many fruits and juices deliver the same sugars in the same ratios to the same tissues within the same time frame to the same metabolic pathways” [88]. Recent work, comparing the acute (first 60 minutes)

tested these assertions [89]. Participants (n = 7), in repeated measures design, ingested 595 mL water with

- nothing - control,
- 6% fructose,
- 6% glucose,
- 6% sucrose, and
- 6% combined fructose and glucose solutions, which is similar to HFCS.

The findings (Table 10) support the notion that, during the 60 minutes following intake, the two multi-saccharide preparations fructose + glucose, representing HFCS, and sucrose elicit similar gut and metabolic responses. This indicates that the acute metabolic impact of HFCS and sucrose are equivalent and supports White’s assertion that sugar and HFCS are equivalent [88]. In addition, the study demonstrates that changes in the plasma are different for fructose and glucose, fructose increases plasma fructose and lactate levels but not glucose, whereas glucose increases plasma glucose but not fructose or lactate. As noted above, lactate reduces renal uric acid excretion, so

fructose ingestion increases SUA and decreases renal urate excretion. In contrast, the uric acid derived from purine rich food increases SUA but does not change the renal urate excretion. The results of this study are consistent with the above research investigating the effect fructose and glucose separately ingested in drinks, at 25% of total energy consumption, for 10 weeks [7, 8].

Table 10 Comparison of acute postprandial effects of fructose, glucose and sucrose [89].

Factor	Fructose	Fructose/Glucose	Sucrose	Glucose
Gastric emptying	0	0	0	0
Ghrelin	0	0	0	0
Glucose dependent insulinotropic polypeptide	0	↑	↑	↑
Glucagon like peptide-1	0	0	0	0
Plasma glucose	0	↑	↑	↑
Plasma fructose	↑	↑	↑	0
Plasma lactate	↑	↑	↑	0
Triglycerides	0	0	0	0

0 = no change, ↑ = increase

A study investigated whether the fructose found in apples (410 g) has the same effect on SUA as apple juice (340 ml), or an equivalent amount of free fructose (26.7 g) and glucose. It reported that after 30 minutes the fructose/glucose control increased SUA by 15 µmol/L (95% CI: 10, 21 µmol/L), apples increased SUA by 19 µmol/L (95% CI: 8, 30 µmol/L) and apple juice increased SUA by 17 µmol/L (95% CI: 9, 24 µmol/L). These increases were equivalent leading the authors to conclude that the SUA increases following ingestion of fructose, regardless of source [9].

In the literature there is a convergence of two streams of research:

- uric acid impacts the body negatively as serum levels insufficient to cause gout, and
- fructose consumption increases SUA, which is associated with a wide range of modern diseases and that the overconsumption of fructose can now be considered a risk factor for the metabolic syndrome [5].

Despite the above reports on SUA there is no clear causal link between fructose intake and metabolic disorders such as diabetes, obesity and the metabolic syndrome. Some researchers have suggested that the causal factor may be upregulated XO activity rather than increased SUA [1] while other researchers have suggested that the causal factor may elevated intracellular uric acid [29].

4. Treatment

The last 15 years of research has provided the clinician with many leads for helping patients both to avoid and manage many of modern diseases of civilisation. Clinical management of SUA involves controlling food intake [4] and where appropriate supplementation with therapeutic agents.

Even assessing SUA and urinary measurements after treatments is complicated. As it is thought that SUA levels are kept in check by renal urate excretion [36], an increase in renal excretion may

reflect increased uric acid production, if not accompanied by a decrease in SUA. Thus, both measures of SUA and renal excretion need to be considered before either of the measurements can be interpreted. A further complication is that reduced intestinal excretion may boost renal excretion, as happens with the genetic polymorphisms of ABCG2 intestinal secretory transporter [36].

5. Dietary Approach

Limiting the intake of fructose-rich and purine-rich foods can be aided using the food tables (Table 2-8). Purine-rich foods have been scored by the original researchers 1 to 5 [4] and the current author has scored fructose levels similarly. This approach allows clinicians to make simple recommendations, such as to restrict intake to food scores 1 and 2, as well as, presenting patients a simple regime. Additionally, the score system may give hope to the patient that with improvements, a wider range of foods will become available. Furthermore, it allows patients to choose which foods to consume and gives a reason for avoiding some foods. Importantly, the amount of a food is also significant as 200 g of a food contains twice as much fructose/purines as 100 g.

Previously dietary advice regarding purine content has been generalised (Table 1) [20] and involved the avoidance of all meat and seafood. While this advice may have helpful in acute situations, the current availability of more accurate purine and fructose levels (Table 2-8) means that individuals can chose a less restrictive long-term diet. For example, choosing chicken thigh instead of chicken breast, or beef and lamb instead of trout.

The DASH diet is suitable as a complete dietary recommendation [90]. The DASH diet was designed to lower blood pressure [91], but it has also been shown to lower SUA and the incidence of insulin resistance [92]. The DASH diet involves low salt intake, high dairy, fruit, grain and vegetable intake and the limitation of fish/meat to one to two servings of 75 g per day. The DASH diet is ideal for people looking for a complete dietary package with recipes etc. The DASH diet is popular in many countries and cookbooks are available in various languages using local foods.

Some aspects of the DASH diet have an established effect on SUA. Firstly, the low intake of fish/meat ensures a low purine intake, yet it is important that adequate protein is consumed to meet the required level intake of 0.8 g/kg/day, necessary to avoid loss of muscle mass, loss of physical function and negative nitrogen mass. This is particularly important for women 50+ years, a group where close to 10% are protein deficient [93]. Significantly, a low protein diet, with “just enough” protein, does not provide the benefits associated with a higher-protein intake such as:

- the maintenance of bone mass and integrity;
- the preservation and the enhancement of muscle mass and function with weight loss and aging; and
- post-absorptive and postprandial glycaemic regulation [93].

The regular intake of eggs and pulses, both relatively high in protein and low in purines, can help to maintain adequate protein intake. Secondly, calcium, found in dairy foods and encouraged in the DASH diet, has been shown to be inversely associated with SUA and gout [4]. Lastly salt, although the DASH diet reduces salt it does not avoid salt. Salt restriction to 2 g daily for 5 days can dramatically increase SUA by 2mg/dl, so extreme restriction of salt is unwise [94].

When the aim is to lower SUA, it is possible to modify the DASH diet by lowering the ingested fructose content – avoiding apples, bananas, dates, grapes, kiwi fruit, pears and all dried fruits. Regarding meat, many cuts of beef, pork and mutton/lamb contain less purines than chicken breast and some fishes such as trout. Thus, there is little truth to the adage "avoid four legged animals to prevent gout".

Gout is associated with the consumption of beer and liquor but not with wine drinking [95]. The risk of gout is significantly raised even with low alcohol daily intakes of 10·0–14·9 g and increases with increasing consumption, so that the risk of gout is 2·5 times higher among men who consume 50 g or more of alcohol daily, compared with non-drinkers [95]. Acute episodes may be more likely to occur with intoxication rather than with moderate drinking, because alcohol is converted to lactic acid which competitively inhibits uric acid secretion at the proximal tubule [25]. Similarly, increases in SUA result from the consumption of beer and liquor but not with the drinking of wine [96]. Beer had greater effects than liquor in both studies and is likely due the purine content of beer. Brewing yeast is very high in purines [4] even though the purine levels in European and Japanese beers is only 5 – 12 mg/dl [38, 97].

There is evidence showing that diets rich in polyphenols, and particularly flavonoids, play a role in the prevention of type 2 diabetes [98]. Cherries (*Prunus avium* L.), have a reputation for reducing arthritic symptoms and gout, which is supported by the two studies. Following the consumption of 280 g cherries by a group of healthy women, average age 30 years, the post-ingestion urinary urate level increased by 70% at 3 hours while the SUA decreased by 15% at 5 hours [99]. In a study of gout suffers, those consuming cherries or cherry extract for two days had a 35% reduced risk of suffering a gout attack [100]. The cherries, in the first study, contained 163 mg/100g phenolics of which 42% were hydroxycinnamates [99]. It is possible that it was the hydroxycinnamates that were responsible for the increased renal excretion of uric acid. Besides being found in sweet cherries, hydroxycinnamates are found in fruits: apples blueberries, cranberries, grapefruit, lemons, oranges, peaches, pears, plums; vegetables: lettuce, potatoes and spinach; coffee and tea [101]. Cherries contain particularly high amounts of one hydroxycinnamate, 3-caffeoylquinic acid. Levels of 3-caffeoylquinic acid are similarly high in plums and some filtered roasted coffees [102]. Caffeoyl quinides are produced during the roasting of coffee beans, and are responsible for coffee's bitter taste [103]. Bilberries (*Vaccinium myrtillus* L.), the European blueberry, contain very high levels of anthocyanidins, 250 mg/100 g. However, when 330 ml bilberry juice was ingested over four weeks, SUA levels did not change [104]. For more information the reader is referred to recent reviews of polyphenols for the metabolic syndrome and a listing of antioxidants/polyphenols in foods [98, 101].

The drinking of lemon juice, squeezed from two lemons in two litres of water daily, has been reported to reduce SUA. After 6 weeks, SUA was reduced by 1.6 mg/dl and urinary pH increased by 1.3 in gout patients. While in individuals with hyperuricaemia, SUA reduced 1.3 mg/dl and urinary pH increased by 1.5 [105].

6. Therapeutic Agents

The wide range of symptoms in metabolic syndrome may be explained by individual genetic predispositions, some suffers get gout, others insulin resistance, etc [106]. There are three possible mechanisms by which hyperuricemia can be reduced:

1) Inhibition of XO which reduces the rate at which purines are metabolised to uric acid [24].
2) Enhancing renal excretion of uric acid [24];
3) Enhancing intestinal excretion of uric acid [53].

7. Pharmaceutical Approach

Together with dietary therapy, the American College of Rheumatology recommends XO inhibition therapy, with either allopurinol or febuxostat, as the first-line pharmacologic urate-lowering therapy in gout. SUA levels should be reduced to improve the signs and symptoms of gout, with a SUA target of <6 mg/dl, and if possible <5 mg/dl. The starting dosage of allopurinol should be no greater than 100 mg/day, and even less with moderate to severe chronic kidney disease [24]. Allopurinol reduces uric acid synthesis by competing with the xanthines for XO. It is given orally and has a half-life of 2-3 hours. Its use is limited to long-term therapy as it can exacerbate an acute gout attack [107]. If the target SUA cannot be meet XO inhibitors, then an oral uricosuric drug should be used in conjunction with the XO inhibitor [24]. Uricosuric drugs, such as probenecid, act on the proximal tubule of the nephron to increase uric acid excretion. It is given orally and has its peak effect after 3 hours. Uricosuric drugs are used to prevent rather than treat gout attacks [107].

For acute attacks colchicine, an alkaloid, is frequently used. It acts by inhibiting the migration of neutrophils in the joints, by binding them to tubulin. It is used to both relieve and prevent attacks of gout and its peak effect occurs one hour after oral administration. It excreted both by the kidneys and the gut [107]. Colchicine is derived from seeds and corms of *Colchicum autumnale* and the pain killing effects of this plant were known to the ancient Greeks [19]. Colchicine treatment is potentially toxic, with initial symptoms of diarrhoea, nausea, vomiting and abdominal pain. It should be administered with great care to the elderly or debilitated patients as cumulative toxicity can occur. Further, it should be used carefully in patients with cardiac, hepatic, renal or gastrointestinal disease. It is avoided in pregnancy, except for women with familial Mediterranean fever. It is administered in a series of doses till either relief or overdose occurs. In the UK, the first dose is 1 ml followed by 0.5 mg every 2-3 hours with a maximum dosage of 6 mg [108]. The non-steroidal anti-inflammatory drugs diclofenac, naproxen, piroxicam, but not ibuprofen, may also be used for the pain during an acute attack [107].

8. Nutritional Supplements

Nutritional supplements to reduce SUA may focus on inhibiting XO, enhancing intestine excretion or enhancing renal excretion. However, little is known about intestinal uric acid elimination and renal elimination involves many genes, so what works for one individual many have no effect on another individual.

8.1 Amino Acids

L-glutamine: this amino acid has been shown to increase renal acid secretion, even at low doses of 2 g (28 mg/kg), presumably due to increasing glomerular filtration rate [109]. L-glutamine is the major fuel for the enterocytes, which produce the intestinal digestive juices, and it supports small intestine integrity and function. L-glutamine contributes to facilitating cell proliferation, limiting

the inflammatory response and apoptosis, and modulating intermediary metabolism through specific transcription factors [110]. Thus l-glutamine works both at kidneys, to eliminate uric acid, and in the intestines, to support the secretion of uric acid in the digestive juices. L-glutamine is well tolerated and doses of 14 g/day are considered safe [111]

L-arginine works together with l-glutamine in the small intestine to facilitate cell proliferation, to limit the inflammatory response and apoptosis, and to modulate intermediary metabolism through specific transcription factors [110]. L-arginine is the source of nitrogen in the production of the endothelial relaxing factor, nitrogen oxide (NO), which impacts on blood flow and blood pressure. Endothelial dysfunction, characterized by decreased NO bioavailability, is the first stage of coronary artery disease [87]. *In vivo* research indicates that uric acid markedly decreases NO release by increasing arginase activity [87]. In contrast, the polyphenols group, mentioned above, appear to inhibit arginase activity [112]. L-arginine also has pronounced glucoregulatory and insulinotropic effects [113]. Thus l-arginine is important for supporting a range of disorders related to elevated serum uric acid. L-arginine is well tolerated and doses of 20 g/day are considered safe [111]. On the practical side, l-arginine base is better tolerated by some with poor digestion but when taken as a powder, in water, it tastes metallic, so the taste of l-arginine HCl is preferable even if acidic.

Taurine is important for kidneys, where it provides osmolar buffering to prevent damage from high osmotic pressures. The highest expression of taurine enzymes are found in the straight tubes of the kidneys [84]. Taurine has been shown to improve glucagon activity, promote glycaemic stability, improve insulin secretion and have a beneficial effect on insulin resistance. Taurine has been observed to be effective in treatments against diabetic hepatotoxicity, vascular problems and heart injury in diabetes [114]. Taurine is well tolerated and doses of 3 g/day are considered safe [111].

8.2 Minerals

Main text Magnesium citrate – this combination contains two substances that have kidney stone inhibiting effects. The building of kidney stones is promoted by high SUA [115].

- Magnesium: an increased intake of magnesium has been reported to be was associated with a decreased hyperuricemia risk. Average magnesium intake in American adults has been reported at only 70-75% of the recommended daily allowance [116].
- Citrate: one report concluded that the treatment with potassium citrate of metabolic abnormalities seen in patients with hypocitraturia, or “unduly acidic urine pH”, corrected the abnormal values and was associated with a very high remission rate of stone disease [117].

Although potassium citrate is frequently used by urologists [117] , magnesium citrate may be clinically preferable, as excess potassium intake may cause heart palpitations. Dosage based on magnesium content is 250-300 mg twice daily reducing to 250-300 mg/day for longer periods.

Sodium bicarbonate ($NaHCO_3$) 2,000 mg twice daily has also been reported to increase urinary pH in diabetes type 1 adults and reduce uric acid crystallisation [82].

8.3 Vitamins

Ascorbic acid or Vitamin C has been shown to decrease SUA. In a group of non-smokers, a dose of 500 mg daily for two months decreased SUA by 0.5 mg/dl. The SUA reduction was likely the

result of an increased glomerular filtration rate [118]. Notably for the hyperuricaemia participants, SUA >7 mg/dl, SUA levels reduced by a mean of 1.5 mg/dl. Similarly, a meta-analysis reported that ingestion of 500 mg Vitamin C, for on average a month, reduced mean SUA by 0.35 mg/dl [119].

8.4 Polyphenols

There is evidence showing that diets rich in polyphenols, and particularly flavonoids, play a role in the prevention of type 2 diabetes [98]. Polyphenols may protect the circulatory system from the damage due to increased arginase activity resulting from elevated SUA levels [87]. Various polyphenols have been shown to decrease arginase, restore endothelial dysfunction and elevate NO levels [120].

Quercetin, a flavonol polyphenol, ingested at 500 mg for four weeks, has been reported to reduce SUA levels in males with a higher than normal levels of SUA. The reduction in SUA was greatest for the individuals with the highest SUA measures. Measures of fasting blood glucose, 24-hour uric acid clearance and blood pressure were unaffected. It was suggested that the most likely mechanism for the SUA reduction was a direct inhibition of XO activity [121]. To put this dosage of quercitin in perspective: in Japan the average daily intake of quercetin is 16 mg [122]. Large amounts of flavonols are rarely found in in foods and if so, the content is highly variable. For example (units: mg/100 g): yellow onions 3-120, red onions 4-100, red wine 2-30, parsley 8-10, green tea 3-9 and blueberries 2-16. Doses of 1000 mg/d quercetin have produced side effects [123]. Quercetin is a flavonol aglycon and its glycoside is rutin. Markedly, in rats the absorption of rutin is considerably faster than quercetin [124] indicating that quercetin needs to conjugated prior to intestinal absorption. This finnding suggests that for optimal absorption quercetin is best taken together with food.

9. Herbals

9.1 Traditional Hypothesis

It is to be expected that traditional herbal treatments will exist for treating gout but not the metabolic syndrome. This because gout has been an easily recognised disease for thousands of years [19] whereas the metabolic syndrome was only been defined in 2001 [125]. Most reports on the use of herbals for metabolic syndrome commonly focus on a single aspect of the metabolic syndrome, in contrast, this paper will review herbal treatments for gout as these may reduce SUA.

Before presenting the treatment material, the concept of evidence-based medicine needs to be addressed. In a perfect world, research into all herbal remedies would be undertaken, as herbal medicine is an integral part of human culture. Currently there are minimal resources allocated for herbal research, due at least partly to commercial considerations, as natural substances are not patentable. A recently published evidence-based herbal, *Herbs and Natural Supplements Volume 4*, recognised only one herb as a treatment for gout, Cranberry (*Vaccinium oxycoccos*) [126]. While this may be correct from an evidence-based perspective, it ignores the worldwide wealth of traditional knowledge including the *WHO monographs on selected medicinal plants* [127]. In contrast, in the two books of traditional European usage, *British Herbal Pharmacopoeia 1983* and *The Complete German Commission E Monographs*, both present more than 10 herbs each [16,

128]. Regardless of the lack of studies on herbal treatments of gout, there is a wealth of clinical experience in Europe.

Many of the herbals used to treat gout act by increasing renal excretion and these preparations are referred to as diuretics. Herbal diuretics act differently to synthetic diuretics. Synthetic diuretics reduce the reabsorption of sodium ions, which increases the volume of the urine and decreases body fluids. Synthetic diuretics are used for renal failure, hypertension and oedema. On the other hand, herbal diuretics have no effect on sodium or chloride ions, rather they contain hydrophilic molecules, which increase the volume of urine such as polysaccharides, saponins, polyphenols and essential oils [129].

The herbs listed in the *British Herbal Pharmacopoeia 1983,* for the treatment of gout, are listed in Table 11. These herbs can be divided into two groups: diuretic and analgesic, but it is only the diuretic herbs that may act to reduce SUA. Clearly this list is not exhaustive and different traditions will have their own local treatments, but this author lacks the competence to discuss other traditions. The author has positive experiences using *Apium graveolens* together with *Urtica dioica herba* and l-glutamine for treating gout. This combination resolved chronic conditions and produced periods of remiss for many years, suggesting that XO activity have been inhibited, as well as, kidney activity promoted. The use of *Urtica dioica herba* for gout has also been noted in central European traditions [130].

Table 11 Traditional herbal treatments for gout listed in the British Herbal Pharmacopoeia, with likely mode of action, either diuretic or analgesic, and phytochemical groups likely responsible for their action [16].

Herb	Common name	Part	Diuretic action	Analgesic action
Articum lappa	Burdock	Root	Polysaccharides	
Apium graveolens	Celery	Seed	Essential oils	
Calluna vulgaris	Heather	Flowers	Polyphenols	
Daucus carota	Wild carrot	Herb	Essential oils	
Eupatorium purpureum	Gravel root	Root	Essential oils Polyphenols	
Populus gileadensis	Balm of Gilead	Leaf buds		Topical: salicins
Guaiacum officinalis	Lignum vitae	Heartwood	Resins	
Harpgophytum procumbens	Devil's Claw	Tuber		Iridoid glycosides
Mentha pulegium	Pennyroyal	Herb		Topical: essential oils
Salix alba	White willow	Bark		Salicins
Sassafras albidum	Sassafras	Root bark	Essential oils	
Teucrium chamaedrys	Germander	Herb	Essential oils Polyphenols	
Trigonella foenum-graecum	Fenugreek	Seed		Topical: polysacchrides

9.2 Evidence-based

When healthy young adults ingested of 330 ml cranberry juice, urinary pH decreased and renal urate increased [131]. This result seems at odds with previous information, that renal urate decreases as urinary pH decreases. A possible explanation is that the pH of the participant group was already relatively high at 6.35. Thus, cranberry juice may be of value as a preventative measure but may not be of value in acute treatments.

Ingestion of 1000 mg curcumin daily was investigated in a group with Non-alcoholic Fatty Liver Disease [132]. Non-alcoholic Fatty Liver Disease is closely associated with the metabolic syndrome and fructose intake [73]. The study reported serum decreases of total cholesterol, low-density cholesterol, triglycerides and uric acid [132]. Curcumin is derived from the spice turmeric (*Curcuma longa*) and has been extensively researched in human trials [133]. It has hepaprotective and cholagogic effects, so it is not unexpected that curcumin has a positive impact on liver diseases [134]. The effect on SUA is however, unrelated to curcumins hepatic effects, rather curcumin derivatives have been shown to be potent dual inhibitors of XO and the urate transporter, URAT1 [135]. The Non-alcoholic Fatty Liver Disease study suggests that 1000 mg curcumin supplies sufficient derivatives to have a clinical influence on SUA, even though there are questions regarding the absorption of curcumin [136]. An additional benefit of curcumin treatment is that it has a protective effect on the kidneys [137].

In healthy young adults, green tea extract has been shown to reduce both SUA and renal excretion of uric acid, suggesting that green tea inhibited XO activity. Doses studied over two weeks were derived from 2, 4 and 6 g *Camellia sinensis*, 62.5 mg/g epigallocatechin. Average changes in SUA were small < 0.2 mg/dl (< 5%) whereas the reduction in renal clearance were approximately 30%. [138].

10. Increasing Intestinal Uric Acid Excretion

It appears that the secretions produced for digestion are the mechanism by which intestinal uric acid excretion occurs. L-glutamine is the preferred fuel for the enterocytes [139], as well as increasing renal pH, and therefore becomes the treatment of choice to support intestinal tissue health. Adequate postprandial hyperaemia is required to produce the intestinal secretions. In cases of inadequate postprandial hyperaemia, such as postprandial hypotension and gastroparesis, the bitter herbs *Artemisia absinthium* and *Gentiana lutea*, may be used to support the systemic circulation, by increasing peripheral resistanc, during postprandial hyperaemia [140].

In addition to ensuring that uric acid is secreted, it is important that it is either degraded to or excreted in the faeces. A high fibre diet, such as the DASH diet, would support both the microbiota nutritionally and act as a carrier for the uric acid. Specific adsorbents such as clay and charcoal are also of interest.

In mice, montmorillonite (bentonite) clay adsorbs uric acid and promotes the diffusion of uric acid from blood vessels to intestine, prevents absorption of uric acid in intestine and decreases SUA [141]. In mice with induced colitis, the processed calcium montmorillonite clay product, Novasil, reduced systemic markers of inflammation, and improved both weight gain and the intestinal microbial profile [142]. Aflatoxin levels in the serum and the urine of adults have been reported to decrease following the consumption of Novasil [143], indicating that the clay is acting

as an adsorbent *in vivo*. Clay, administered at the doses 1.5 g and 3 g daily for 3 months, was reported to have no effect on the serum values of a wide range of vitamins and minerals, although strontium did increase at the higher dosage [144]. A recent review suggested there were no major toxicity problems associated with bentonite clay [145], however care should be taken to ensure that clay products are suitable for human internal use before consumption.

Activated charcoal is another adsorbent. It is used in single doses of 50 g to treat many forms of gastrointestinal poisoning [108]. Coconut shells or peat are burnt i.e. "activated" with gases at a high temperature to remove previously adsorbed substances and to reduce particle size. The final product is exceptionally porous with a surface area up to 3500 m^2/g. In contrast to bentonite clay, this process produces a product inherently free of contaminants. *In situ,* charcoal adsorbs drugs and toxins through weak intermolecular forces, with non-ionized, organic compounds binding more avidly than dissociated, inorganic ones [146]. In older patients (mean age 84 years) with end-stage renal disease, SUA decreased when treated with a low protein diet and 30 g activated charcoal for 10 months, without evidence of hyponatremia or hyperkalaemia [147]. A group of 23 patients, on maintenance haemodialysis and suffering from severe chronic uremic pruritus, were treated with activated powdered charcoal (6 g/day). In 10 patients the pruritus disappeared completely, while in another 10 there was partial improvement [148]. In another study with chronic uremic pruritus, contrasted to placebo, charcoal 6 g daily for 8 weeks, relieved pruritus subjectively in all but one patient (P= 0.01). Symptomatic relief from pruritus coincided with objective resolutions of active, scratch-induced skin lesions (P= 0.03). Importantly there was no change in serum lipids, alkaline phosphatase, phosphorus, or calcium, during the treatment with charcoal and no adverse effects were noted [149]. Activated charcoal has also been successfully used in trials, at the lower dose of 1 g/day, to treat intestinal gas [150]. The question of whether the absorption of vitamins is affected during activated charcoal therapy, as vitamins are organic compounds, has been answered: a study where 16 g activated charcoal was ingested for 3 weeks, reported no change in serum levels of vitamins A, D and E [151]. Thus activated charcoal can be considered a safe remedy for long term use but, it still may interfere with the uptake of some pharmaceuticals and therefore should be taken at least 3 hours away from the pharmaceuticals [152].

A presentation of evidence-based treatments for reducing elevated SUA is found in Table 12.

Table 12 Evidence-based treatments for reducing elevated SUA with suggested doses.

Treatment	Kidney activity	Intestinal excretion	XO inhibitor	Endothelial support	Suggested daily dosage
Activated charcoal [147, 148]		X			500 - 6000 mg
L-Arginine [87, 110]		X		X	1500 - 6000 mg
Ascorbic acid [118, 119]	X				500 - 2000 mg
Bentonite clay [141]		X			1500 - 3000 mg
Cherry juice [99]	X				150 - 250 ml
Citrate [117] (Magnesium)	X				1000 - 2000 mg
Cranberries [131]	X				250 - 350 ml
Curcumin [132]	X		X		500 – 1000 mg
L-Glutamine [109, 110]	X	X			2000 - 7500 mg

Lemon juice [105]	X			2 lemons
Magnesium [116](citrate)	X			200 - 300 mg
Quercetin [121]		X	X	500 mg
Salt [94]	X			> 2000 mg
Sodium bicarbonate [82]	X			2000 - 4000 mg
Taurine [114]	X		X	1000 - 2000 mg
Tea – green [138]		X		2000 - 4000 mg

XO = xanthine oxidoreductase

11. Areas Requiring Clarity

In this review there have been numerous conflicting themes presented by various researchers. Until these are resolved, the complex role of uric acid in the body will not be fully understood. Examples of these conflicting viewpoints and unknown areas include:

1) If kidney activity tightly controls SUA [36] why does the use of XO inhibitors allopurinol or febuxostat decrease SUA [24]? Is kidney activity influenced by XO inhibitors?

2) On the one hand, dietary intervention can change SUA by 1-2 mg/dl [20] while on the other hand SUA is tightly controlled by XO levels and kidney activity [36]. These two statements appear contradictory.

3) The digestion of purines in the gut yields uric acid [1] and dietary interventions change SUA by 1-2 mg/dl [20]. Why is the uric acid produced in the gut not degraded completely in the gut, as is the uric acid secreted by the intestine [56]? Do high levels of exogeneous uric acid block the flow of SUA through the intestine to the gut? Can adsorbents be consumed with high purine foods to prevent increasing SUA?

4) Do adsorbents retain uric acid, so that it is excreted in the faeces, or do they enhance exposure of uric acid molecules to uricolytic bacteria.

5) What influences uricolytic bacteria?

6) The small intestine may be considered as a “third kidney” in discussions of uric acid excretion. How is excretion influenced by diarrhoea, constipation, probiotics, prebiotics, fibre and pharmaceuticals?

7) The importance of compromised intestinal elimination in the development of gout and kidney stones has yet to be established.

8) Why are beer and spirits associated with gout and elevated SUA but not wine?

9) Is a high fructose diet, particularly during gestation and infancy, benign? Hyperuricaemia in hypertensive pregnancy identifies women at increased risk of adverse maternal and foetal outcome [153]. While a study, with mice, reported that a high fructose during pregnancy induced insulin resistance, hyperleptinemia, and plasma oxidative stress in male, but not female, progeny [154].

12. Limitations

The author works in a clinical practice not as a researcher and cannot be considered an expert in many of the areas covered in this paper. This review has been written primarily for clinicians in the fields of integrative and complimentary medicine, with only undergraduate training, rather than specialists in the areas of gout, diabetes and cardiovascular disease. Thus, the physiology

section, presented at a basic level for non-specialists, may seem overly basic to experts in these areas.

The food tables focus on foods, rather than food products. Some limited information on the fructose content of food products is available from the relevant references whereas, information on purines/ uric acid content is largely limited to foods.

The number of clinical studies conducted with the various nutrients and herbals is often limited often to a single study, within a specific group, and this makes it difficult to generalise or predict treatment outcomes. Hopefully this compilation of potential treatments will stimulate further research with these substances, as well as, extending the knowledge base of clinicians.

Many of the dietary areas covered in this review are both incompletely researched and difficult to research so, we may need to wait generations for definitive answers. This raises ethical questions regarding how much proof is required before giving dietary advice. Regarding this dilemma, Frank Hu wrote "we should devote our efforts to obtaining the best possible scientific evidence while keeping an open and constructively sceptical mind" [3].

13. Conclusion

This article reviews the current knowledge regarding foods and food products which increase serum uric acid and a range of treatments that reduce serum uric acid. Serum uric acid levels are of clinical importance because elevated levels are associated with a wide range of metabolic, renal and cardiovascular disorders [63]. Fructose, rather than glucose, in the artificial sweeteners sugar and HFCS, has been shown in 10-week long studies to have a negative impact on metabolic and cardiovascular parameters [7, 8]. In addition to uric acid, the metabolism of fructose produces a range of toxic inflammatory compounds which negatively affects multiple body tissues [5]. Consequently, measures of SUA may not accurately reflect the intracellular toxicity resulting from fructose ingestion [29]. Avoiding foods high in purines (Table 1-4) and following the WHO guidelines regarding the intake of free sugars can be expected to lower SUA levels.

- In both adults and children, WHO recommends reducing the intake of free sugars to less than 10% of total energy intake (strong recommendation).
- WHO suggests a further reduction of the intake of free sugars to below 5% of total energy intake (conditional recommendation).
- Free sugars include monosaccharides and disaccharides added to foods and beverages by the manufacturer, cook or consumer, and sugars naturally present in honey, syrups, fruit juices and fruit juice concentrates [155].

The use of preparations for lowering SUA should be been clinically viewed primarily as an adjunct to dietary control.

Author Contributions

Michael McMullen has completed all the work.

Competing Interests

The authors have declared that no competing interests exist.

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