

## 01402471 Nutritional Biochemistry

ชีวเคมีโภชนาการ  
ภาคปลาย 2560  
ครั้งที่ 9 วันที่ 26 มี.ค. 2561

## Biotin & Pantothenic acid

- Biotin (B7) เป็น cofactor ของเอนไซม์ 5 ชนิด  
ถ่ายโอน CO<sub>2</sub> (คาร์บอกเนตอิสรระ) ไปยัง  
substrate
- Pantothenic acid (B5) เป็นองค์ประกอบของ  
cofactors 2 ชนิดคือ CoA และ Acyl Carrier  
Protein ของ fatty acid synthase

- Biotin เป็นวิตามินละลายน้ำได้ อยู่ในกลุ่ม  
วิตามิน B รวม ค้นพบโดยบังเอิญเมื่อปี 1927  
Boas สังเกตว่าหนูที่ได้รับไข่ขาวแห้งเกิดโรค  
ผิวหนัง scaly dermatitis ขนร่วงและมีอาการ  
ผิดปกติของระบบประสาท
- ไข่ขาวมีไกลโคโปรตีน avidin ที่จับกับ biotin
- Mammals ไม่สามารถสังเคราะห์ biotin ได้  
ต้องได้จากอาหารที่สังเคราะห์โดยจุลินทรีย์และ  
พืช

Benefits of Vitamin B7 or Biotin		Organic Facts
		Maintains good health of skin and hair
		Helps maintain blood sugar levels in body
		Aids in weight loss and stimulating metabolism
		Good for ensuring proper functioning of heart
		Beneficial for growth and maintenance of muscle tissues

**HEALTH BENEFITS OF VITAMIN B5 OR PANTOTHENIC ACID**

Provides relief from body fatigue & builds stamina

Helps reduce stress, depression & anxiety

Regulates cholesterol levels & controls blood pressure

Strengthens immune system

Assists liver in metabolizing toxic substances

Helps to increase hemoglobin level

Helps maintain healthy skin & hair

Relieves from asthma, autism & Parkinson's disease

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## Vitamin C

- Ascorbate และ Ascorbic acid
- เกี่ยวข้องกับปฏิกิริยามากมายทั้ง enzymatic และ nonenzymatic
- เช่น hydroxylation ในกระบวนการสังเคราะห์ collagen
- ป้องกันเซลล์จาก ROS
- ใช้รักษาโรคมะเร็ง ?

- วิตามินซี สังเคราะห์ได้ในพืชทุกชนิด พบมากในผลไม้และผัก
- การปรุงอาหารทำให้สูญเสียวิตามินซี
- ใช้วิตามินซีเติมลงในผลิตภัณฑ์อาหารเพื่อรักษาความสดและยืดอายุการเก็บรักษา
- L-ascorbic acid สังเคราะห์ได้ ราคาไม่แพง
- วิตามินซีมีผลเล็กน้อยในการป้องกันโรคไข้หวัด (common cold) แต่อาจจะช่วยลดความรุนแรงของโรคและระยะเวลาสั้นลง

**BENEFITS OF VITAMIN C** Organic Facts

- Helps to prevent scurvy
- Helps to cure lead toxicity
- Effective in curing cataracts
- Aids in lowering hypertension
- Relieves symptoms of asthma
- Prevents cancer and heart diseases
- Protects against cough and common cold

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## Fat-soluble vitamins

- วิตามิน K มาจากคำว่า *koagulation* (ภาษาเยอรมัน)
- ในอาหาร พบมากจากพืชในรูป phylloquinone (K1)

### VITAMIN K

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• Vitamin K helps blood clotting, essential to stop bleeding from wounds.

• People with vitamin K deficiency may experience easy bruising, nosebleeds, etc., although the deficit of this vitamin is rare to occur.

• The sources of vitamin K are animal fats (egg yolks, whole milk, red meat, ...) and dark green vegetables (spinach, asparagus, ...)



## VITAMIN E BENEFITS, SOURCES & DEFICIENCY

Vitamin E acts as an antioxidant and is required to protect cells against oxidative damage from free radicals, for example oxidation of the lipids in cell membranes. By limiting free-radical production and possibly through other mechanisms, vitamin E might help prevent or delay the chronic diseases associated with free radicals.

RDA: 15 mg | Fat-soluble Vitamin

### BENEFICIAL FOR

- ✓ Improves Immune Function
- ✓ Improves Brain Function
- ✓ Protects Heart Health
- ✓ Protects Eyes and Lungs
- ✓ Protects Against Some Cancers
- ✓ Beneficial for Serious Athletes

### FOOD SOURCES OF VITAMIN E

Nuts, sunflower seeds, almonds, hazelnuts, peanuts, spinach, broccoli, mango and tomato. Nut butters and oils such as sunflower oil, safflower oil and peanut butter also provide vitamin E, and so do wheat germ oil, corn oil and soybean oil.



### VITAMIN E DEFICIENCY

Existence of dietary vitamin E deficiency is not considered to be a problem even in people consuming a relatively poor diet. Deficiency only occurs in people with severe fat malabsorption and rare genetic disorders.

## VITAMIN A BENEFITS, SOURCES & DEFICIENCY

Vitamin A helps maintain healthy eyes, skin, teeth, and bones. It's also essential for cell division, which means renewal, and it plays a key role in keeping our immune system strong. Our body doesn't need much vitamin A, and too much (in supplement form) can harm your health, so it's best to get our A the natural way: from plenty of fruit and vegetables.

RDA: 700 mg | Fat-soluble Vitamin

### BENEFICIAL FOR

- ✓ Bones and Teeth
- ✓ Powerful Antioxidant
- ✓ Combat free radicals
- ✓ Healthy Eyes

### FOOD SOURCES OF VITAMIN A

Carrots, sweet potatoes, pumpkin and squash, red bell pepper, spinach, cantaloupe, mango, broccoli



### VITAMIN A DEFICIENCY

Poor night vision; dry, rough, or cracked skin; dry mucous membranes including the inside of the eye; slow wound healing; nerve damage; reduced ability to taste, hear, and smell; inability to perspire; reduced resistance to respiratory infections.

## VITAMIN D BENEFITS, SOURCES & DEFICIENCY

Vitamin D improves immune function for everybody and prevents colds, flu and pneumonia. We get most of our vitamin D from sunlight on our skin. The vitamin is made by our body under the skin in reaction to summer sunlight. Vitamin D makes a healthy babies with strong immune systems, it also reduces the risk of premature birth.

RDA: 600 mg | Fat-soluble Vitamin

### BENEFICIAL FOR

- ✓ Reduces influenza infections
- ✓ Improves heart function
- ✓ Speeds wound healing
- ✓ Lower risk of fractures

**Vegan and Vegetarians** usually obtain vitamin D from the action of sunlight on the skin or by taking fortified foods such as soy milk, margarine and vitamin supplements which are made from yeast or other fungi. Fortified vegan products contain D2 (ergocalciferol). Foods with naturally occurring vitamin D usually contain animal derived vitamin D3 (cholecalciferol).

### FOOD SOURCES OF VITAMIN D

Salmon (especially wild-caught), Mackerel (especially wild-caught), Mushrooms, Tuna canned in water, Sardines canned in oil, Milk or yogurt fortified with vitamin D, Egg yolks, Cheese



### VITAMIN D DEFICIENCY

A lack of vitamin D can lead to bone deformities such as rickets in children and bone pain and tenderness as a result of a condition called osteomalacia in adults. Symptoms of deficiency include Osteoporosis, Depression, Obesity, Backache, Multiple sclerosis, Cancer, Hypertension and Diabetes.

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## REVIEW ARTICLE

# The association of vitamin C, alcohol, coffee, tea, milk and yogurt with uric acid and gout

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### Abstract

About 2500 years ago, gout was observed by Hippocrates and many people suffered severe pain and deformity. Lifestyle and diet play a significant role in gout and serum uric acid levels. Epidemiological and research studies have supported this evidence. Many recommendations and guidelines from different parts of the world mention the impact of diet on gout. Recently, new research has shown associations between vitamin C, alcohol, coffee, tea, milk and yogurt with uric acid and the risk of gout. Our review summarizes recently published research regarding dietary impact on the risk of gout and serum uric acid levels.

**Key words:** Gout, uric acid, diet.

### INTRODUCTION

Gout is an inflammatory arthritis and is associated with high serum uric acid (SUA).<sup>1,2</sup> It is relatively common in late middle-aged men<sup>3,4</sup> and women,<sup>5,6</sup> with increased rates in menopausal women.<sup>4,7–9</sup> In the USA, the incidence of gout is 8.4 per 10 000 persons/year.<sup>10</sup> Many factors contribute to gout risk, such as high SUA,<sup>1</sup> ethnicity,<sup>11–13</sup> underlying disease,<sup>14–17</sup> age,<sup>18</sup> greater body mass index,<sup>19</sup> and so on. Many studies based on the Third National Health and Nutrition Examination Survey (NHANES-III) suggest that dietary consumption affects SUA levels which is parallel to the increase in the risk of gout.<sup>20</sup> The relationship between diet, drinking and gout was found a long time ago.<sup>14,21–23</sup> In this review, we will update the recent data of the association between vitamin C (VC), alcohol, tea, coffee, milk and yogurt with SUA and gout risk as shown in Table 1.

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### VITAMIN C

A recent cross-sectional study in Korea showed that the intake of VC is lower in subjects with hyperuricemia when compared with control groups.<sup>24</sup> The effects of VC on SUA and the uricosuric effect are evaluated in many studies.<sup>25–32</sup> One randomized controlled trial showed that SUA levels were significantly reduced with supplementation of 500 mg/day of VC for 2 months, and VC is beneficial in the prevention and management of gout.<sup>30</sup> In 2011, a meta-analysis of randomized controlled trials, concluded that the median dose of VC supplementation (500 mg/day) significantly lowered SUA.<sup>31</sup> In contrast, Stamp *et al.*<sup>29</sup> studied the effect of supplemental VC on SUA in patients with gout. This study was a pilot randomized controlled trial: 40 patients with gout and a SUA level of more than 6 mg/dL were included. This research did not observe any significant effect of VC when compared to allopurinol on the reduction of SUA, and the uricosuric effect was small in patients with gout, regardless of whether VC was administered alone or in combination with allopurinol. Reasons for this result include: the uricosuric effect of VC is weak, the dose of VC was small, and there might be interactions with other medications (in

Diet	Serum uric acid		Risk of gout	
	Change	Condition	Change	Condition
Vitamin C	↓	500 mg/day <sup>3</sup>	↓	> 500 mg/day <sup>4</sup>
Coffee	↓	≥ 4 cups/day <sup>5,6</sup>	↓	≥ 4 cups/day <sup>7,8</sup>
Tea	–	Any drinks <sup>6</sup>	–	Any drinks <sup>7,8</sup>
Alcohol				
Beer†	↑	≥ 0.01 serving/day <sup>9</sup>	↑	≥ 2 servings/week <sup>11</sup>
Liquor/spirits†	↑	≥ 0.1 serving/day <sup>9</sup>	↑	≥ 1 servings/month <sup>11</sup>
Wine†	↓	< 1 serving/day <sup>9</sup>	–	Any drinks <sup>11</sup>
Sake	↑	≥ 20 drinks/week‡ <sup>10</sup>	No study	
Shochu	↑	Any drinks <sup>10</sup>	No study	
Milk	↓	≥ 1 serving/day <sup>12</sup>	↓	≥ 2–4 glass/week§ <sup>13</sup>
Yogurt	↓	≥ 0.5 serving/day¶ <sup>12</sup>	↓	≥ 2 cups/week†† <sup>13</sup>

†Increased risk of gout attack; ‡1 drink is 11.5 g of ethanol for sake; §skim milk or low fat milk; ¶or ≥ once every other day; ††adjusted for age-adjusted relative risk. ↑, increase; ↓, decrease; –, no change.

**Table 1** Recent data of the association between vitamin C, alcohol, tea, coffee, milk and yogurt with serum uric acid and the risk of gout

particular, aspirin and diuretics). This paper does not support VC supplementation as a urate-lowering therapy in gout patients. Many studies suggested mechanisms of VC for reduced SUA. First, at the renal urate transporter URAT1 and a sodium-dependent anion co-transporter SLC5A8/A12, VC has a uricosuric effect.<sup>31,33–35</sup> Second, it increases renal fractional clearance of uric acid.<sup>25</sup> Finally, VC decreases free radical-induced damage to body cells, thereby reducing SUA.<sup>32,36</sup>

The relationship between VC and incidence of gout was assessed by one prospective study in 2009.<sup>33</sup> This study concluded that the incidence of gout decreased with increasing VC intake with up to a 45% lower risk at the top VC intake category of 1500 mg or more. So, higher VC intake is independently associated with a lower risk of gout, and supplemental VC intake may be beneficial in the prevention of gout.<sup>33</sup>

Although much of the research has studied the relationship between VC and SUA, no research has evaluated the role of VC in gout flare. Some authors are aware that taking large amounts of VC may trigger gout flare because of changes in SUA.<sup>25</sup>

## COFFEE

Coffee is the most widely consumed beverage in the world. In the US, the relationship between coffee and the incidence of gout in men and women was shown in two cohort prospective studies.<sup>37,38</sup> The risk of gout in men whose intake of coffee was 4–5 cups/day and ≥ 6 cups/day was 40% and 59% lower, respectively, when compared with no coffee consumption. The

association between total caffeine intake and risk of gout was not significant.<sup>38</sup> The risk of gout was 22% and 57% lower in women whose intake was 1–3 cups/day and ≥ 4 cups/day, respectively, compared with no coffee consumption, but, in contrast to men, there was a significantly inverse association between total caffeine intake and risk of gout.<sup>37</sup> So, long-term coffee consumption is associated with a lower risk of gout incident,<sup>34,37,38</sup> and components other than caffeine may inversely affect the association between coffee and gout.<sup>37,38</sup>

Moreover, coffee has not been found to affect SUA. In 1999, the first study of the relationship between coffee consumption and SUA concentration was published.<sup>39</sup> This study concluded that coffee drinking may be associated with lower concentrations of SUA. Based on 14 758 participants ages > 20 years in NHANES-III (1988–1994), Choi and Curhan<sup>40</sup> evaluated the relationship between coffee, tea and caffeine intake, and SUA levels. These findings suggest that coffee consumption is associated with lower SUA levels. Also, this study suggested that the inverse association with coffee appears to be due to factors other than caffeine. Another study in Japan showed inverse associations between coffee consumption and both SUA levels and hyperuricemia in men, but not in women, regardless of adjustment for the covariates. After allowance for confounding factors, women showed a statistically significant inverse association between coffee and SUA levels.<sup>41</sup> A study in Asia showed that coffee consumption (≥ 4 cups/day) is associated with lower SUA levels.<sup>42</sup> Several mechanisms have suggested that coffee consumption may affect the risk of gout and

SUA.<sup>20,34,39–41,43,44</sup> From the review study, we have concluded that coffee consumption ( $\geq 4$  cups/day) has urate-lowering properties and reduces the risk of gout. There has been no research study between coffee and gout flare.

Because coffee intake is one of the independent risk factors for chronic kidney disease<sup>45</sup> and is associated with increased risk of fractures in women,<sup>46</sup> drinking coffee for lowering the risk of gout should be considered carefully.

## TEA

Tea is a leaf of *Camellia sinensis*. There are many types of tea. It can be divided into six major types of reprocessed basic tea leaf depending on fermentation, such as green tea, blue tea, black tea, yellow tea, white tea and dark tea.<sup>47</sup>

In tea, phenolic compounds (mainly tea catechins) are the main chemical components.<sup>48</sup> Five tea catechins can inhibit the liver enzyme xanthine oxidase.<sup>49</sup> In contrast to coffee, the relationship between nonspecific types of tea and SUA and risk of gout is negative for both men and women.<sup>37,38,40</sup> For green tea, a recent study has shown that daily drinkers of green tea exhibited a dose-dependent and statistically significant four-fold increase with hyperuricemia,<sup>42</sup> but an earlier study has shown that green tea drinking did not show a statistically significant trend with SUA.<sup>39</sup> During fermentation of black tea, the oxidized derivatives of black tea catechins, theaflavin and thearubigins are formed.<sup>50</sup> Theaflavins can inhibit the activity of xanthine oxidase.<sup>50,51</sup> The relation between black tea and SUA was shown in 2010 by Bahorun *et al.*<sup>52</sup> This data showed that black tea intake significantly decreased SUA by 9.4% and 7.1% in male and female groups with highest baseline values, respectively.<sup>52</sup> In contrast, with recent data published in 2013, Teng *et al.*<sup>42</sup> showed that there was no significant association between consumption of black tea and SUA levels. In our opinion, differences in baseline SUA levels between the studies may be a cause of the conflicting results. There has been no research investigating the impact of tea on gout flare.

As mentioned above, there are many types of tea. Some studies do not classify the type of tea, and a few studies only showed the relationship between green tea or black tea and SUA. Different types of tea may give different results, other specific types of tea need to be evaluated in the future. There is conflicting data with black tea and SUA.

## ALCOHOL

Alcohol has been recognized as a potential risk factor for increased SUA and gout flare. An association between increased alcohol intake and hyperuricemia and risk of gout has been shown in many studies.<sup>53–57</sup> In 2013, a meta-analysis with 42 924 participants assessed the relative risks (RRs) and dose response of gout risk to alcohol consumption. The RRs for light ( $\leq 1$  drink/day), moderate ( $> 1$  to  $< 3$  drinks/day) and heavy drinking ( $\geq 3$  drinks/day) versus no or occasional alcohol drinking were 1.16 (95% confident interval [CI], 1.07–1.25), 1.58 (95% CI, 1.50–1.66) and 2.64 (95% CI, 2.26–3.09), respectively. The results suggest that alcohol consumption is associated with increased risk of gout.<sup>58</sup>

### Beer, liquor/spirits

Beer has a high content of purine guanosine, which can increase uric acid production.<sup>21</sup> In 2004, the relationship between intakes of beer, liquor and wine, and SUA levels was evaluated.<sup>54</sup> The results showed that SUA levels increased with beer or liquor intake, and the authors concluded that the effect of individual alcoholic beverages on SUA levels varies substantially: beer confers a larger increase than liquor, and increase in SUA with beer intake was more pronounced for women than for men. Yu *et al.*<sup>59</sup> also demonstrated that beer intake is independently associated with increased risk of hyperuricemia in men. In 2010, Gaffo *et al.*<sup>55</sup> showed that, compared with non-drinkers, significant associations between higher SUA concentrations and greater beer intake were observed among men and women. However, in men there were only significant findings in the higher category of intake at a median of 12 servings/week (one serving of beer is equal to a 12 ounce bottle, approximately 355 mL). An association between greater liquor intake and higher SUA concentrations was only found in men in the last year of the study.

In their study, Choi *et al.*<sup>53</sup> used questionnaires to investigate the relationship between alcohol consumption (including beer and spirits) and risk of gout incident in 47 150 male participants with no history of baseline gout. Beer consumption showed the strongest independent association with the risk of gout, and the multivariate RR increased with servings of beer per week and per day. Consumption of spirits was also significantly associated with gout. They concluded that alcohol intake is strongly associated with an increased risk of gout and varies substantially according to type of

alcoholic beverage: beer confers a larger risk than spirits, even though alcohol content per serving was less for beer than spirits. At present, there has been no research evaluating the relationship between SUA or risk of gout and 'light beer.' Hence, we conclude that beer and spirits increase the risk of gout.

### Wine

Regarding the difference between wine and other alcoholic beverages in relation to SUA and risk of gout, Choi and Curhan<sup>54</sup> showed that SUA levels decrease with increasing wine intake, except for the top category ( $\geq 1$  serving per day) in which the level was lower than that of no use. They concluded that moderate wine drinking ( $< 1$  serving per day) does not increase SUA levels. However, these findings contrast with the study of Gaffo *et al.*<sup>55</sup> Their data showed that wine intake was not associated with SUA in either sex.<sup>55</sup> The relationship between risk of gout and wine has been prospectively confirmed. Data from a prospective study investigating alcohol intake and risk of gout incident in men showed that the RR for men who drank  $\geq 2$  glasses of wine per day compared with those who drank less than one glass per month was 1.05 (95% CI 0.64–1.72), and there was no significant trend with increasing levels of wine consumption ( $P$  for trend = 0.66). Regardless of the type of wine, this association still persisted. It can be concluded that in men, moderate wine drinking (118 mL serving per day) was not significantly associated with an increased risk of gout.<sup>53</sup> However, there have been no studies investigating the relationship between gout risk and wine drinking for women.

### Sake and shochu

Sake is a Japanese rice wine containing ethanol. Shochu is a Japanese distilled spirit, also containing ethanol, that is made from barley, sweet potato, rice or any combination. For sake, a 6-year prospective study conducted by Nakamura *et al.*<sup>56</sup> showed a dose-response between drinking sake and risk of hyperuricemia. For shochu, a study by Sugie *et al.*<sup>57</sup> showed there was no statistical difference in the risk of hyperuricemia when compared with subjects who drank sake, beer and shochu. Both sake and shochu cause increased SUA, but there was no data for gout flare.

Although beer and liquor have been associated with the risk of gout incident, wine has not. However, in 2014, there was a prospective, internet-based, case-crossover study which examined the quantity and type of alcohol consumed and risk of recurrent gout attacks

over the prior 24 h. This study showed a significant dose-response relationship between the amount of alcohol consumption and risk of recurrent gout attacks.<sup>60</sup> Consuming wine, beer or liquor was associated with significantly increased risk of gout attack. This study concluded that even a moderate amount of alcohol consumption, regardless of type of alcoholic beverage, was associated with an increased risk of recurrent gout attacks.<sup>60</sup> Many recommendations and guidelines suggest avoiding drinking alcohol.<sup>61–66</sup>

### MILK AND YOGURT

A numbers of studies have shown an association between milk and yogurt with SUA and gout.<sup>27,67–71</sup> Choi *et al.* studied the relationship between SUA and dairy products, including milk and yogurt. This study showed a significant inverse relationship between those who consumed milk one or more times per day and SUA level compared with no milk drinking. It also found a significantly lower SUA level in those who consumed yogurt at least once every other day compared with those who did not consume yogurt.<sup>27</sup> Similarly, Zgaga *et al.*<sup>70</sup> showed that skimmed milk and low-calorie yogurt had a significant and inverse association with SUA concentration. For the association between yogurt and milk with risk of gout in men, a prospective study showed that for men who drank two or more glasses of skim milk per day as compared with men who drank less than one glass per month, the multivariate RR was 0.54 (95% CI, 0.40–0.73;  $P$  for trend  $< 0.001$ ).<sup>68</sup> The risk of gout had a similar inverse association with the level of consumption of low-fat yogurt.<sup>68</sup> From this evidence, milk and low-fat yogurt may decrease SUA and the risk of gout. Milk products such as skim milk powder enriched with glycomacropptide and G600 milk fat extract may reduce the frequency of gout flares.<sup>67</sup>

Multifactorial analysis can explain the association between milk and SUA and reduced gout flare. First, orotic acid in milk promotes renal urate excretion.<sup>70</sup> Second, milk contains casein and lactalbumin, both of which have been shown to decrease SUA via a uricosuric effect.<sup>71,72</sup> Third, both glycomacropptide, the 64-amino acid carboxyterminal fragment of  $\kappa$ -casein, and G600 milk fat extract, a complex lipid fraction in which the phospholipids and gangliosides, particularly disialo ganglioside 3, have anti-inflammatory effects in acute gout and may reduce gout flares through inhibition of the inflammatory response to monosodium urate crystals in the joint.<sup>67,69</sup> Finally,

vitamin D is found in milk, and a study suggests that gout patients may have significantly lower levels of 1,25-(OH)<sub>2</sub>-vitamin D<sub>3</sub>. After administration of urate-lowering drugs in this study, there was a decrease in SUA which was associated with a significant elevation in the levels of 1,25-(OH)<sub>2</sub>-vitamin D<sub>3</sub>.<sup>73</sup> The supplementation of vitamin D to prevent hyperuricemia has not been studied.<sup>74</sup>

## CONCLUSION

Although many studies show association between VC, alcohol, coffee, tea, milk and yogurt with SUA and gout, in the 2012 American College of Rheumatology Guidelines, they recommend only avoidance of alcohol overuse (defined as more than two servings/day and one servings/day for men and women, respectively) and limiting of alcohol, particularly beer, and also wine and spirits, in gout patients.<sup>62</sup> Other than that, they encourage only low-fat or non-fat dairy products in gout patients.<sup>62</sup> Beyond the scope of gout, we should consider other risk factors and possible benefits in other diseases.

## AUTHOR CONTRIBUTIONS

Patapong Towiwat reviewed the literature and drafted the manuscript; Zhan-Guo Li proofed the manuscript.

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