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EFFECT OF PHYSICAL ACTIVITY *Fast Interval Training* AND PROVISION OF SKIN MELINJO EXTRACT (*Gnetum gnemon*) ON EXPRESSION URAT1, GLUT9 AND SGLT2 IN HYPERURICEMIA INSULIN RESISTANCE

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ABSTRACT

Observational studies and randomised controlled studies suggest Increased prevalence of hyperuricemia is a decrease in physical activity and high consumption of purines. Disruption of urate reabsorption causes changes in the main functions of transporter proteins in the proximal tubule membrane. One of them is the intake of URAT1 and efflux by GLUT9 and also for the expression of SGLT2. Insulin resistance causes disturbances in glucose uptake in (SGLT2) and urate. The mechanism of glucose uptake can be mediated by exercise and effect of melinjo skin extract. A Technical Expert Panel (TEP) of 2 medical specialist and expertise of disorder the urinary system performed the review using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) model. The TEP planned a research on PubMed selecting "Hyperuricemia" as MeSH (Medical Subject Headings) term adding to PubMed Search Builder the terms "Exercise" and "Melinjo skin extract". TEP is considered for eligibility articles published within the last 10 years, including original research, in particular in vitro studies, and animal and clinical studies in English. Results: Of the 90 identified studies, TEP included 15 studies, 8 animals, and 4 clinical studies and 3 Review. Conclusion: Our scoping review describes and summarizes the important role of exercise and the effect of melinjo peel extract in modulating uric acid levels, Insulin resistance and up-and-down regulation of urate transporters

Introduction

Hyperuricemia is caused by an increase in urate in the blood from the normal limit of urate in the blood. Hyperuricemia can occur due to an increase in uric acid production caused by a high-purine diet or due to the breakdown of nucleic acids that exceeds normal limits or even due to a combination of both. Based on epidemiological studies, the condition is included in the category of hyperuricemia, namely when the serum uric acid level in adults is at a level exceeding 7.0

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mg/dL in men and exceeding 6.0 mg/dL in women (Kim et al., 2010; Putra, 2006; Lamb et al., 2006).

Management of hyperuricemia follows several pillars, namely providing education, physical activity, dietary therapy and also providing pharmacological interventions. Based on hyperuricemi management, the pattern of handling hyperuricemia for handling interventions in the form of pharmacological interventions is only carried out if non-pharmacological interventions are not successfully implemented (Lai et al., 2017; Mezza et al., 2012)

The state of uric acid caused by the stimulation and response to hyperglycemia in the long term causes disturbances in the metabolism of sorbitol. Sorbitol as the intermediate product of the conversion of glucose to fructose whose mechanism is catalyzed by the enzyme aldolase reductase. Decreased glucose levels then turn into sorbitol which is then converted to fructose. Meanwhile, in hyperglycemia, the accumu lation of sorbitol in nerve cells causes the atmosphere to become hyperosmotic, causing the entry of extracellular fluid into the cytoplasm of nerve cells. This situation causes swelling of the Schwann cells and damage (Hao et al., 2015).

Obesity is often associated with insulin resistance and is also closely related to free fat levels. There are four general causes of insulin resistance that can cause it. Insulin resistance in obesity causes glucose intolerance accompanied by hyperinsulinemia, so that in a hyperinsulinemic state, this situation causes a reduction in the excretion of uric acid and sodium by the kidneys so that urate levels in the blood will rise.

Material and Methods

This scoping review was carried out following PRISMA-ScR (*Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scope Overview*). The first step is creation of a technical expert panel (TEP) consisting of 2 specialist doctors with expertise in the field of disorders physiology and urinary system. All TEP components are confident with scoping review methodology. As a search strategy, TEP planned research on PubMed (Public MedLine, run by .) National Center for Biotechnology Information, NCBI, of the Bethesda National Library of Medicine, Bethesda, MD, USA), chose the term “hyperuricemia” as MeSH (Medical Subject Headings); follower terms added to run PubMed Search Builder: "uric acid", "uric acid mlevel" ("insulin resistance"; “exercise” and and “Melinjo skin extract”. According to the purpose of the review, TEP defines the characteristics of sources of evidence, considering the feasibility of every study published in the scientific literature in the last 10 years (last update in June 2021), including original articles, revie in particular in vitro, in silico and animal studies and clinical studies in English and Indonesian.

Results and Discussion

From the 90 identified studies, 60 articles were screened for eligibility after removing duplicates and 30 articles irrelevant to the purpose of the scoping review. This, 15 were excluded for different reasons because based on the study there was still not much discussion about the relationship of exercise with uric acid and specific transporters. Of these, only 15 studies were included (Figure 1). We divided our results in preclinical and clinical studies (Table 1).

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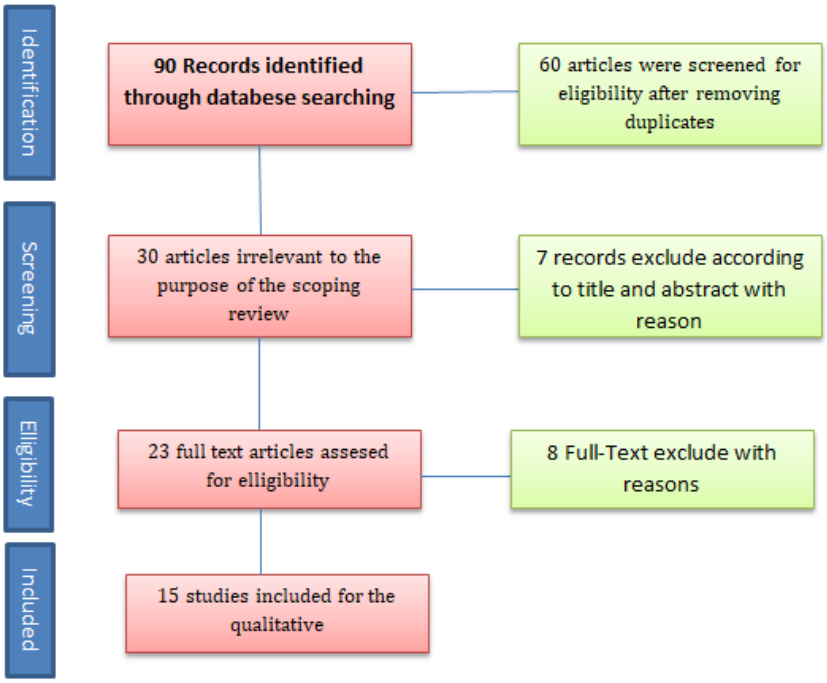

Figure 1. Flow diagram of selection process review

Table 1. Relevant data from each study included scoping review

Author, Year	Design	Main Results
Andriyani, 2021	Animal Study	High fructose intake resulted in a significant decrease in ABCG2 expression compared to the control group because in the condition of the model given fructose (hyperuricemia) GLUT9 played a role in the excretion and excretion of glucose in the kidneys.
Dhimas, 2020	Animal Study	High purine consumption showed a significant decrease in uric acid levels in the gout group which was treated with melinjo skin extract at a dose of 100 mg/KgBW, 200 mg/KgBW and 300 mg/KgBW. The dose of melinjo skin with 300 mg/KgBW showed a maximum decrease until the final treatment
Hasan, 2020	Animal Study	There was a significant decrease in uric acid levels in the gout group which was treated with melonjo peel extract at a dose of 450 mg/KgBW and 900 mg/KgBW. The dose of melinjo peel with 900 mg/KgBW showed a maximum decrease until the final treatment
Machrina, 2019	Animal Study	there is an increase in the distribution of the insr gene (insulin receptor) which is greater after giving physical activity with the type of fast interval training (FIT) compared to other types of physical activity although the results show a distribution of the insr gene after physical activity
Kahka, 2020	Animal Study	showed a decrease in blood glucose levels in type 2 diabetes patients, and a decrease in insulin resistance index after giving physical activity with the Fast Interval Training type. FIT is also one of several types of interval training recommended by the Advisory Committee on Medicines Scheduling (ACMS).
Mount, 2016	Animal Study	Based on the analysis using immunohistochemistry, it can be seen that URAT1 is located in the apical membrane of the proximal tubule which was studied based on research that has been carried out both in humans and rats as experimental animals that have a

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		relationship between the increase in uric acid and the expression of URAT 1
Ghezzi et al., 2018	Review	SGLT2 plays a role in glucose reabsorption, many scientific studies discuss the development of drugs that work as SGLT2 inhibitors in hyperglycemic patients, another result found is a decrease in blood uric acid levels for all SGLT2 inhibitors
Yinqiu et al., 2020	Review	Physical activity in hyperuricemic patients is influenced by insulin resistance conditions that cause hyperglycemia and also hyperinsulinemia causes a decrease in insulin resistance which affects the level of glucose reabsorption of SGLT2 and also GLUT9 will be affected as well as the reabsorption of URAT-1
Kudo et al., 2021	Clinical Study	Aerobic Interval Training (AIT) has an increasing effect on stimulation of insulin sensitivity compared to continuous moderate intensity. The HOMA-IR index value is the basis for determining the level of insulin sensitivity by comparison using a baseline. There was an increase in gene expression of PGC1α vasus lateralis 138% (p=0.001) and maximal sarcoplasmic reticulum calcium uptake increased to 50%
Guido et al., 2021	Review	Differences in glucose uptake in insulin resistance with the parameters studied based on glucose dependent and glucose independent gave the effect of increasing both after giving physical activity 24 to 48 hours
Stanford and Goodyear, 2014	Clinical Sudy	Muscle contractions on physical activity and insulin can have an activating effect of Akt on skeletal muscles. Activity from muscle contractions causes an increase in P-Akt and also in 160 and 250 Kda proteins, PAS immunoreactivity occurs. Phosphorylation on Akt substrates is important in providing insulin bioeffect and muscle contraction for subsequent signal transduction processes to provide translocation of GLUT9
Yeong, Ng, 2018	Animal Study	SGLT2 inhibitors are blocked so that sugar levels will be taken for uptake by GLUT9 Isomer 2 to be excreted and excreted into the urine so that the urate level in the blood decreases.
YuZhang, 2014	Animal Study	SLC2A9 in the proximal tubule provides information on an increase in urate levels which has the potential to cause hyperuricemia and also causes impaired excretory function of urate.
Koivula et al., 2020	Clinical study	Physical activity causes excessive glycogen disassembly and increases the enzyme activity of Glucose 6 Phosphate which occurs repeatedly which causes an improvement in the levels of the Glucose 6 Phosphatase enzyme and a shift in the need for ATP for the glycogen cycle in exercise so that the need for ATP for the formation of purine metabolism will be deficient so that purine metabolism decreased and decreased uric acid levels
Roshan et al., 2020	Clinical study	Serum Uric Acid and Obesity has directional associations. The present study has concluded that increase uric acid related to high risk of obesity. These results give brief results for the clinical practice of the usage of uric acid as a predictor of obesity.

Abbreviations **:** FIT (*Fast Interval Training*), *Sodium Coupled glucose Transporter* (SGLT), *uric acid transporter 1* (URAT1), glukosa transporter 9 (GLUT9), Adenine Tri Phosphate (ATP), Aerobic Interval Training (AIT), Homeostatic model assessment- Insulin resistance (*HOMA*-IR) , Solute carrier family 2 Numbe A 9 (SLC2A9)

Insulin Resistance and Hyperuricemia

Insulin resistance can be regarded as one of the promoters of the formation of excess urate levels in the blood which causes hyperuricemia. In a state of insulin resistance can cause a lot of damage to the level of homeostasis in the body associated with metabolic syndrome disease where insulin sensitivity is low in physiological conditions and causes intolerance to glucose so that

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insulin can continuously be formed and increase its levels in physiological conditions resulting in hyperinsulinemia. The state of hyperinsulinemia in addition to causing causative diseases such as dyslipidemia, diabetes mellitus and hypertension, physiologically Hyperinsulinemia also affects the excretion of urate which will disrupt the exchange of urate in transporters which causes urate levels in the blood to increase due to the reabsorption process. In many cases and research studies that have been carried out, patients who experience cases of hyperuricemia have high insulin resistance compared to those in the general population (Roshan, 2020).

Purine Biosynthesis

The energy source used in the synthesis of GMP is ATP while GTP is used for the synthesis of AMP. The presence of the formation branch obtained from the IMP precursor to produce GMP and AMP from the feedback formation reaction of ATP and GTP (Figure 1.) was determined as a determinant of the formation of IMP levels

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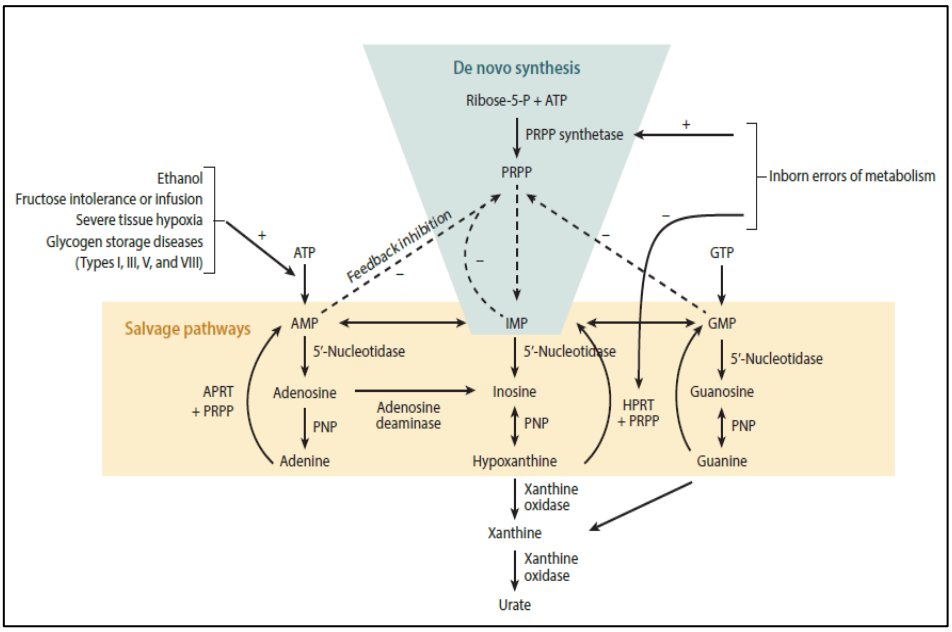

Figure 1. Urate production

The salvage pathway describes the degradation process of nucleic acids with the result that free purines are in the form of adenine, guanine and hypoxanthine through the 5-nucleotidase phosphorylation process. This pathway requires the presence of hypoxanthine and guanine and then increases PRPP thereby increasing nucleotides through the HGPRT reaction

Nucleotide deficiency can be used as an evaluation indicator with the concl usion that the mechanism states that GTP provides energy for ATP synthesis and ATP as a determinant of GTP synthesis. In the urate production line itself, there are two lines that are traversed, namely the Salvage line and the de novo line. (Car oline et al., 2018).

Uric acid transporter in the proximal tubule

Based on further research that has been carried out by GWAS (Genome Wide Association) shows that there is an association between uric acid and dysfunction of the urate-anion transporter which is responsible for the excretion and reupptake of uric acid in the blood. The urate transporter proteins were identified by GWAS mapping and supported by research from (Pavelcopa et a.l, 2020) stated that of all the urate-anion transporter proteins in the proximal tubule The kidneys state that proteins that have a major role in

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influencing uric acid levels in the body are GLUT-9, URAT-1 and ABCG2. The URAT1 protein is encoded by the SLC22A12 gene as a gene that expresses a transporter in the body, where many transporter receptor proteins on the surface of proximal tubular cells such as OAT1 and OAT3 are included in the expression of the SLC22A12 gene that contribute to the transport of uric acid in the kidneys, especially in the secretion and excretion of uric acid. URAT-1 transports urate from the renal tubular lumen to the epithelial cells.

Urate-anion exchange in the proximal tubule

There is an exchange with luminal uric acid whose process is facilitated by URAT-1 or organic aniontransporter 10 (OAT10). Then OAT4 exchanges with the divalent anion. GLUT-9 performs its activities by acting as an exit pathway for uric acid located on the basolateral membrane. The secretion of uric acid causes a series of processes to occur as follows: the entry of uric acid into cells through the basolateral membrane with the occurrence of alpha-ketoglutarate exchange mediated by OAT1 as well as OAT3. In the apical membrane, uric acid is secreted by mabidrug resistance protein (MRP4).

URAT 1 is a protein encoded by the solute carrier family 22 member 12 gene (SLC22A12) which is part of the SLC22 organic transporter URAT1 is also part of OAT. Based on the analysis using immunohistochemistry, it can be seen that URAT1 is located in the apical membrane of the proximal tubule which was studied based on research that has been carried out in both humans and mice as experimental animals (Mount, 2016). At present many studies have been found regarding URAT1 for the treatment of hyperuricemia. Drugs used as URAT1 inhibitors include uricosuric drugs such as probenecid, phenobritat and also losartan. The mechanism of action of the drug is more by inhibiting reabsorption compared to uric acid than uric acid excretion so that it gives the effect of uric acid levels in the blood (Mount, 2016). URAT1 has high affinity for aromatic organic anions such as nicotinamide, pyrazinamide (PZA) and also has low affinity for lactate, beta-hydroxyburiate, acetoacetate and organic ions such as chloride (cl-) and nitrate (Mount, 2016).

In the main study on GLU-T-9, an initial conclusion was given that GLUT-9 was identified as a transporter of fructose with a low affinity level, but the rest is known that GLUT-9 is a uric acid transporter with high affinity (Blu, 2018). For the transporter protein GLUT-9 is encoded by the Solute Carrier Family 2 gene, Facilitated glucose transporter member 9 (SLC2A9) and is also part of the GLUT Hexoses transporter. GLUT-9 in the case of purine and uric acid metabolism serves as the main uric acid exit pathway at the basolateral membrane of the proximal tubule and also functions in the transepithelium of uric acid reabsorption. For other uric acid transporters, OAT1 and OAT3 function in uric acid secretion which is controlled by the proximal tubule so that transport occurs into cells from the interstitium (Mount, 2016)

Reabsorption of sugar/glucose that occurs in the glomerulus is coordinated by 3 different types of proteins, namely: SGLT1, SGLT2 and GLUT2 (Gezzi et al., 2018). SGLT2 in segment 1 and segment 2 prokimal tubules plays a role in glucose reabsorption. The results of reabsorption can reach 90% of the glucose that has been filtered by the glomerulus.

Relationship between insulin and SGLT2, URAT 1 and GLUT9

The state of hyperglycemia causes the kidneys to carry out higher levels of reabsorption in the kidneys. The kidneys can filter glucose levels every day to reach 163 grams of glucose per day. The state of insulin resistance in hyperuricemia causes blood glucose levels to increase and causes the action of SGLT2 to increase expression in the proximal renal tubule. The filtered glucose level reaches 90% will be reabsorbed by SGLT2 in the proximal convoluted tubule while the remaining 10% will be reabsorbed

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by SGLT1 in the descending and ascending tubules.

When giving physical activity to patients with hyperuricemia, which is influenced by insulin resistance conditions that cause hyperglycemia and also hyperinsulinemia causes a decrease in insulin resistance which affects the level of glucose reabsorption of SGLT2 and GLUT9 will be affected as well as the reabsorption of URAT-1 (Yinqiu et al., 2020).

Fast Interval Training and Insulin Resistance

Conducted by (Machrina, 2019) by providing interventions for several physical exercises, namely: Severe Continuous Training (SCT), Moderate Continuous Training (MCT), Slow Interval Training (SIT), Fast Interval Training (FIT). The insr receptor gene in FIT has more gene expression, followed by FIT and MCT and SCT by giving physical activity exercise treatment for 8 weeks. For the HOMA-IR index obtained, the HOMA-IRA index on physical activity training types FIT and SIT showed a decrease in the index value of insulin resistance.

Various studies have been conducted to examine the relationship between the incidence of insulin resistance and the occurrence of cases of hyperuricemia (Andriyani, 2021; Pavelcop et al., 2020; Kushiyama et al., 2016; Fauzi, 2018; Tianshu, et al., 2017). Likewise, physical activity on insulin resistance affects the decrease in uric acid levels in cases of hyperuricemia (Machrina, 2019; Skleryk et al., 2013; Yong Park et al. 2019).

Physical activity in the form of exercise has been shown to have a decreasing effect and can also maintain levels of uric acid (Yong Park, 2019) Decrease insulin resistance, increase carbohydrate, protein and fat metabolism (Andriyani, 2021). Giving physical activity also provides an overview of the formation of glycogen breakdown from exercise so that there is a simplification, formation of lactic acid and also the production of ATP as a signal transduction component that causes increased uric acid formation and also increased excretion of uric acid by the transporter URAT1. However, until now not many have conducted further studies on changes in genetic expression of transporter proteins from Urat such as GLUT9 and also URAT1 in physical activity in the form of sports in Fast Interval Training (FIT) type sports.

Potential of Melinjo skin extract

Based on bioinformatics studies on molecular docking with the basic principles of applying the target protein. It is known that melinjo skin has a target class of oxidoreductase with a percentage of 6.7% which plays an active role in influencing the oxidation work of the xanthine oxidase enzyme by reducing the level of oxidation of the enzyme thereby reducing its mechanism of action in xanthine catabolism to produce the final product in the form of uric acid.

(Hasan et al., 2020) used experimental animal models of hyperuricemic rats by providing an intervention in the form of skin extract from melinjo. Experimental animals apply the gold standard of their research by using control as a comparison and negative control by administering llouprinol to experimental animals. The dose uses allouprinol 90mg/KgBB, while the melinjo peel extract which has been screened for phytochemicals has high levels of saponins and plavonoid compounds. The results of giving the bark extract showed that the effectiveness of the extract was better at 70% in reducing uric acid levels compared to allouprinol which was only 50%.

(Dhimas et al., 2020) using a melinjo skin microencapsulation system. Preliminary tests conducted to screen for bioactive compounds present in the skin of melinjo showed the presence of metabolites of the flavonoid group and also saponins. Evaluation of uric acid levels in the blood was carried out at intervals of hours after giving the extract to rats. The results of the study were analyzed using statistical tests explaining that there was a P value that was smaller than 0.005 and gave a decision that microencapsulation of melinjo

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skin in rats could reduce uric acid levels at 4 hours.

Conclusion

Hyperuricemia is caused by excessive levels of uric acid in the blood, uric acid levels themselves can be caused by high consumption of purines in the body, loss of function in each urate-anion transporter protein, causing loss of urate exchange and intracellular anion does not occur properly. The transporter protein that functions as reabsorption in urate is largely controlled by the main urate transporter, URAT-1 and also reabsorption is controlled by GLUT9 and also exerts a direct expression effect on SGLT2.

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