THE INFLUENCE OF Sauropus androgynus (L.) Merr. LEAVES AND PAPAVERINE ON THE GLUCOSE ABSORPTION AND GLUCOSE METABOLISM IN THE LIVER

Agik Suprayogi.
Department of Anatomy, Physiology and Pharmacology, Faculty of Veterinary Medicine Bogor Agricultural University (IPB), Jl. Agatis-Kampus IPB Darmaga-Bogor-16680, Indonesia, Phone/Fax: 0062-251-629462, email: asupray@ yahoo.com

ABSTRACT
This experiment was to investigate the influence of the Sauropus androgynus (SA) leaves and the role of its papaverine (PPV) content on the glucose absorption and glucose metabolism in the liver. Thirty six male White New Zealand Rabbits divided into three groups of 12 animals each. Three solutions were administrated orally twice a day to each group such as, distilled water to the control group, PPV-hydrochloride solution 0.5 % (2 mg PPV/kg body weight) to the PPV group, and a suspension of ground SA leaves 14.17 % (PPV dose equivalent to 2 mg/kg body weight) to the SA group. After 5 days of application, blood samples at hepatic and portal vein were taken from 4 rabbits of each group by surgery procedure. This procedure was repeated after 10 and 15 days of application. Glucose concentration of serum samples was determined using test Kit. The glucose absorption obviously increased after 15 days of PPV and SA leaves application, it could be seen that glucose concentration in the portal vein enhanced significantly at this time. The administration of SA leaves caused a surplus of glucose in the liver. It was obtained earlier and to a higher extent than after PPV administration. The PPV content of the SA leaves might be plays an important role in the effects of SA leaves.

Keywords: Sauropus androgynus, papaverine, rabbit, glucose, and metabolism

INTRODUCTION
Sauropus androgynus (SA), a member of Euphorbiaceae family, is a leafy shrub found in Malaysia, Indonesia, South-west China and Vietnam. This plant is commonly used as a vegetable. For instance in Taiwan, people usually consume this plant as a vegetable at 6 to 303 g/d per person [1]. Around Kuala Lumpur, Malaysia on 458 families showed that the average consumption of SA was 180 g/wk per person [2].

In Indonesia, mothers eat or drink SA leaves and preparations respectively, in order to increase their breast feeding capacity [3]. For ruminants, SA powder and SA extract administration could enhance milk yield in lactating ewes. The enhancement of milk yield in the cellular level of mammary gland could have been caused by two importance factors such as, first there were increasing of population of secretory cells and the synthetic activities in the secretory cells and seconds, the increase in nutrient supply to the lactating mammary gland [4]. For poultry production, supplementation of SA meal 30 g per day to the broiler diet was effective to improve feed conversion ratio without reducing body weight, besides the supplementation could reduce fat accumulation in broiler chickens [5].
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This experiment was to investigate the influence of the Saururus androgyrus (SA) leaves and the role of its papaverine (PPV) content on the glucose absorption and glucose metabolism in the liver. Thirty-six male White New Zealand Rabbits divided into three groups of 12 animals each. Three solutions were administered orally twice a day to each group such as, distilled water to the control group, PPV-hydrochloride solution 0.6 % (2 mg PPV/kg body weight) to the PPV group, and a suspension of ground SA leaves 14.17 % (PPV dose equivalent to 2 mg/kg body weight) to the SA group. After 5 days of application, blood samples at hepatic and portal vein were taken from 4 rabbits of each group by surgery procedure. This procedure was repeated after 10 and 15 days of application. Glucose concentration of serum samples was determined using test Kit. The glucose absorption obviously increased after 15 days of PPV and SA leaves application, it could be seen that glucose concentration in the portal vein enhanced significantly at this time. The administration of SA leaves caused a surplus of glucose in the liver. It was obtained earlier and to a higher extent than after PPV administration. The PPV content of the SA leaves might be plays an important role in the effects of SA leaves.

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INTRODUCTION

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In Indonesia, mothers eat or drink SA leaves and preparations respectively, in order to increase their breast feeding capacity [3]. For ruminants, SA powder and SA extract administration could enhance milk yield in lactating ewes. The enhancement of milk yield in the cellular level of mammary gland could have been caused by two importance factors such as, first there were increasing of population of secretory cells and the synthetic activities in the secretory cells and seconds, the increase in nutrient supply to the lactating mammary gland [4]. For poultry production, supplementation of SA meal 30 g per day to the broiler diet was effective to improve feed conversion ratio without reducing body weight, besides the supplementation could reduce fat accumulation in broiler chickens [5].

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One of the active compounds of SA was identified as alkaloid papaverine [2]. The alkaloid is known as a vasodilator, relaxant, and a spasmyloytic for various smooth muscle and cardiac tissue. Consequently it has some general effects on the physiological function, particularly on the gastrointestinal tract, cardiovascular system and on the metabolism.

Recent study showed that SA leaves contain 7 major substances [4], which have an important role to increasing milk yield in lactating mammary gland. These substances are five of the polyunsaturated fatty acids, as precursors in the eicosanoids biosynthesis, such as octadecanoic acid, 9-eicosanoic, 5,8,11-heptadecatrienoic acid methyl ester, 9,12,15-octadecatrienoic acid ethyl ester, and 11,14,17-eicosatrienonic acid methyl ester. One substance is a 17-ketosteroid, androstan-17-one,3-ethyl-3-hydroxy-5 alpha which could be involved in the steroid hormone biosynthesis. Another substance, 3,4-dimethyl-2-oxocloponent-3-enylicolic acid could be hydrolyzed to acetate and participate in the citric acid cycle to produce ATP.

The administration of SA leaves aqueous extract 20 % (500 mg/kg BW) directly into abomasum of goats using an implanted catheter for 12 days revealed an increase of the average milk yield by 21.03 % and of glucose metabolism of the mammary gland by 52.66 %. Beside, this investigation showed that the glucose concentration of the blood in SA leaves group was higher than the glucose concentration in the control group [6].

With references to the present fact could be derived the presumption that SA leaves might be influence the glucose metabolism in the liver and/or glucose absorption in the gastrointestinal tract. PPV content of the SA leaves might be one of active compound which has responsible in the effects. Now days, there were still lack of information according to the role of PPV content in the SA leaves on the glucose metabolism in the liver and/or glucose absorption in the gastrointestinal tract.

This experiment investigates the influence of SA leaves on glucose absorption and glucose metabolism in the liver and tries to elucidate the role of PPV in this context.

MATERIALS AND METHODS

Fresh SA leaves from the local markets around Bogor-Indonesia was dried in an automatic oven at 60°C overnight. The dry leaves were ground to powder (SAP). The 42.50 g of the powder were suspended in 300 ml distilled water (14.17 %). Base on the PPV content of 1 kg fresh SA leaves amounts to 5.80 g [2], it presumable that the PPV content in the SAP suspension was 3.33 mg PPV in 1 ml of SAP suspension. Papaverine solution (6 %) was prepared from papaverine-hydrochloride powder (from Kimia Farma Company in Indonesia) in distilled water by dissolving 1 g PPV powder in 20 ml distilled water.

Thirty-six male White New Zealand Rabbits 2.5-3.0 month old with a mean body weight of 1.77 (+0.45) kg were kept indoor individual metabolic cages for 29 days. In the room of the rabbits, a ventilation system with exhaust fans was installed. In a preliminary period of 14 days, all rabbits were adapted to their new environment especially to the metabolic cages and to the pelleted feed before the main experiment period started. The rabbits were fed with commercial pelleted feed and water ad libitum. Intestinal and ectoparasites were controlled by subcutaneous injections of 0.1 ml ivermectine (1 %).

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At the beginning of the main experiment period, all rabbits divided into 3 groups of 12 animals each. Three solution were administered to each group such as, distilled water to the control group (0.67 ± 0.16) ml per animal, PPV-hydrochloride solution 0.5 % (2 mg PPV/kg body weight, 0.76 ± 0.21 ml per animal) to the PPV group, and a SAP suspension 14.17 % (PPV dose equivalent to 2 mg/kg body weight, 0.95 ± 0.14 ml per animal) to the SAP group. All solutions were administered directly into the stomach by oral catheters twice a day in the morning and afternoon. After 5 days application, blood samples at hepatic and portal vein were taken simultaneously from 4 rabbits of each group by surgery procedure using an anesthesic (Ketamin-Hydrochloride). This procedure was repeated after 10 and 15 days of application. From these blood samples, the glucose concentration at hepatic and portal vein could be determined by the 7-glucose-PAP method, using Unimate test Kit.

The glucose concentration in the portal vein can be used as an indirect indicator of the glucose absorption from the gastrointestinal tract. The different between glucose concentration in the portal vein (GP) which enters the liver and in the hepatic vein (GH) which leaves the liver to transport glucose to the systemic stream can show the flux of glucose in the liver [Flux = GP-GH].

Data analysis
Analysis of variance (ANOVA) was used to determine the difference between the treatments means [7]. A probability (P) value less than 0.05 was accepted as significantly different. Duncan’s multiple range tests [8] was used to determine differences between the treatment means.

RESULTS AND DISCUSSION

Glucose concentration in the portal vein: Glucose absorption
The daily oral administration of SAP and PPV has no effect on the glucose concentration in the portal vein during the first 10 days. After 15 days of administration of SAP and PPV the glucose concentration in the portal vein increase significantly (p<0.05) compared with control group (Table 1). It can be supposed that the glucose absorption increase as well. With regard to the nutrient content of the SA leaves [9], the enhancement of glucose absorption seems not to be caused by the content of carbohydrates of the SA leaves which is actually not high but by a physiological and pharmacological effect of the PPV and probably other compounds of SA leaves.

Table 1. Mean of glucose concentration (mg %) in the portal vein after 5, 10, and 15 days of treatment

<table>
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<th>Groups</th>
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<tr>
<td>Control</td>
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Note: Numbers followed by the same letter are not significantly different (p>0.05).

PPV is a potent inhibitor of cyclic nucleotide phosphodiesterase and can increase CAMP, which is implicated as a possible mediator in Beta-adrenergic relaxation of smooth muscle [10, 11]. Like other alkaloid opiates, PPV also causes an alteration of the gastrointestinal motility, usually gut contents are eliminated more slowly and are in contact with the fluid absorbing epithelia of the intestine for longer periods of time [12]. At the same time the mucosal blood flow in the smooth muscle of the gastrointestinal tract is increased [13]. From both facts: lower gastrointestinal motility and increased mucosal blood flow, it can be supposed that the absorption of nutrient will be improved by PPV.

SA leaves have an important influence on the physiological function in the gastrointestinal system. The SA leaves preparation could enhance the contraction force of isolated intestines, while the frequency of motility was reduced [14]. It indicates that SA leaves contain compounds which act like PPV or actually was alkaloid PPV [2].

Other study showed that the administration of PPV induced only a tendency improvement of the digestibility of dry matter, crude protein, crude fiber and ash, presumably raising the dose would cause a stronger effect. Otherwise, the administration of SA leaves increased feed digestibility of nutrient to a higher extent than after PPV application [16].

Glucose metabolism in the liver: Flux of glucose in the liver
Glucose concentration of the hepatic vein can be presented in Table 2, a significant decline can be noticed on the 10th and 15th day of the administration of PPV (p<0.05) if compared with the value obtained on the 5th day of application. Probably, this phenomenon is caused by an inhibitory effect on the gluconeogenesis and/or glycogenolysis in the liver which are two metabolic pathways to increase the glucose concentration of the blood. Referring to the pharmacological action of several drugs, presumably PPV plays an important part as an antagonist (block) of Beta and/or Alpha-adrenergic receptors in the liver. Consequently, noradrenaline as a neuro-transmitter of the sympathetic nervous system can not activate these receptors to induce gluconeogenesis and/or glycogenolysis [10].

The administration of SAP influence the glucose concentration of the hepatic vein like PPV but the significant decrease is obtained already after 5 days of application (p<0.005) compared with values obtained in the control group (Table 2). This might indicate an involvement of the other substances in the SAP which act synergistically with PPV and therefore accelerate its inhibitory effect on gluconeogenesis and/or glycogenolysis. After 10 days and 15 days of application of SAP, the values of the glucose concentration of the hepatic vein contained in the SAP group has tendency return to the control level (p>0.05). It can be supposed that other compounds which have an antagonistic effect on the PPV action in the liver have overcome the former decreasing effect. This experiment can not exactly explain this phenomenon, because there is no information according to which responsible active compounds contained in the SAP.

Table 2. Mean of glucose concentration (mg %) in the hepatic vein after 5, 10, and 15 days of treatment

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The flux of glucose through the liver is presented in Table 3 and Figure 1. The flux of glucose in the control group (Figure 1, A) illustrates the normal situation of the liver. The glucose concentration in the hepatic vein tends to be higher than the glucose concentration of the portal vein during the whole experiment period. It shows the negative flux of glucose which are the differences among glucose concentration reveals significant decline obtained on 15 days of treatment (22.00 ± 4.15) mg % compared with values obtained on the 5 days of treatment (76.50 ± 10.99) mg %. This observation can be understood that the monosaccharides which are absorbed from gastrointestinal tract and are transported to the liver through the portal vein are not only glucose but also galactose and fructose. The galactose and fructose metabolism in the liver converts these monosaccharides to glucose which leaves the liver through the hepatic vein. Other sources of additional glucose might be the gluconeogenesis and glycogenolysis in the liver [16].

The administration of PPV changes the normal situation of the glucose flux in the liver (Figure 1, B). A distinct change occurs after 10 days of treatment when the glucose concentration of the portal vein starts to exceed the glucose concentration of the hepatic vein which causes a surplus of glucose in the liver. The positive flux of glucose occurred on 15 days of treatment significantly is (31.25 ± 10.35) mg % compared to the negative flux of glucose obtained on 5 days of treatment is (74.00 ± 4.80) mg %. The PPV enhances the absorption glucose. Consequently more glucose enters liver than normal but without an increase of amount of effluent glucose. The glucose in the liver can be used in different ways; part of it might be stored as glycogen (glycogenesis), for the synthesis of triglycerides (lipogenesis), and/or for synthesis of amino acids. Besides, the parenchyma cells of the liver demand glucose to sustain their energy metabolism. These metabolic pathways are regulated mainly by insulin [16]. The lack of an increase of efflux as a conceivable consequence of the higher glucose concentration the portal vein might be explained by the physiologically higher stimulation of the insulin release by the glucose itself.

Table 3. The flux of glucose (mg %) in the liver [Flux = GP-GH] in control group, PPV group, and SAP group after 5, 10, and 15 days of treatment

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<th>Groups</th>
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<tbody>
<tr>
<td></td>
<td>5 days</td>
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</tr>
<tr>
<td>Control</td>
<td>-76.50 ± 10.99a</td>
<td>-44.50 ± 26.23a</td>
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The administration of SAP (Figure 1, C) lead to the same situation as the administration of PPV, but its effect seems to be faster and stronger. The effect of SAP on the glucose flux in the liver creates a faster and stronger effect PPV. It can be seen that SAP administration reduces the glucose concentration in the hepatic vein significantly already 5 days after application, this is an earlier effect than that induced by PPV. The negative flux of glucose significantly reduce already after 5 days of application is (11.56 ± 2.23) mg % compared to the negative flux on the control group is (76.50 ± 10.99) mg %. At the same time, the glucose concentration in the portal vein increases sharply to a significantly higher value on the 15th day of application. This situation changes glucose flux in the liver from negative flux to the positive flux on the 15th day of application significantly is (51.75 ± 11.89) mg % compared to the negative flux of glucose obtained on 5 days of treatment is (11.56 ± 2.23) mg %. The positive flux also significantly higher when compared to the positive flux obtained in PPV group on 15th days of application. Consequently the administration of SAP creates the surplus of glucose in the liver much faster and stronger than PPV administration.

Figure 1. The flux of glucose in the liver [Flux = GP-GH] in control group (A), PPV group (B) and SAP group (C)

Generally, this study is in accordance with the previous research. The influence of consuming SA leaves on the lactating goats showed that it could stimulate the mammary gland metabolism, accordingly the milk synthesis was increased [6]. It can be supposed that the increase of milk synthesis requires a higher amount of precursors of milk compounds. The consuming of SAP had higher contribution to the increase in nutrient supply to the mammary gland of lactating ewes (as indicated by total VFAs concentration in the portal vein) than consuming of its extract [17]. The investigation shows that the administration of SAP can enhance the glucose absorption from gastrointestinal tract and also surplus of glucose in the liver much faster and stronger than PPV administration. Probably the PPV content in the SAP plays an important part in this action, but it can be supposed that there are still one or more other substances which cooperate with PPV. The increase of glucose metabolism in the liver in the study might be as an attempt to provide the precursors of milk compounds and/or fulfillment of energy metabolism for increasing the proliferation of lactating mammary gland cells and their synthetic activities [4].

CONCLUSIONS

The influence of the oral administration of SAP suspension 14.17 % (PPV dose equivalent to 2 mg/kg body weight, 0.95±0.14 ml per animal) and PPV-hydrochloride solution 0.5 % (2 mg PPV/kg body weight, 0.78±0.21 ml per animal) on the White New Zealand Rabbits twice a day

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</table>

Note: Numbers followed by the same letter are not significantly different (p>0.05).

The administration of SAP (Figure 1, C) lead to the same situation as the administration of PPV, but its effect seems to be faster and stronger. The effect of SAP on the glucose flux in the liver creates a faster and stronger effect PPV. It can be seen that SAP administration reduces the glucose concentration in the hepatic vein significantly already 5 days after application, this is an earlier effect than that induced by PPV. The negative flux of glucose significantly reduce already after 5 days of application is (11.55 ± 2.23) mg % compared to the negative flux on the control group is (76.50 ± 10.99) mg %. At the same time, the glucose concentration in the portal vein increases sharply to significantly higher value on the 15th day of application. This situation changes glucose flux in the liver from negative flux to the positive flux on the 15th day of application significantly is (51.75 ± 11.89) mg % compared to the negative flux of glucose obtained on 5 days of treatment is (11.55 ± 2.23) mg %. The positive flux also significantly higher when compared to the positive flux obtained in PPV group on 15th day of application. Consequently the administration of SAP creates the surplus of glucose in the liver much faster and stronger than PPV administration.

![Figure 1. The flux of glucose in the liver (Flux = GP-GH) in control group (A), PPV group (B) and SAP group (C).](image)

Generally, this study is in accordance with the previous research. The influence of consuming SA leaves on the lactating goats showed that it could stimulate the mammary gland metabolism, accordingly the milk synthesis was increased [6]. It can be supposed that the increase of milk synthesis requires a higher amount of precursors of the milk compounds. The consuming of SAP had higher contribution to the increase in nutrient supply to the mammary gland of lactating ewes (as indicated by total VFAs concentration in the portal vein) than consuming of its extract [17]. The investigation shows that the administration of SAP can enhance the glucose absorption from gastrointestinal tract and also surplus of glucose in the liver much faster and stronger than PPV administration. Probably the PPV content in the SAP plays an important part in this action, but it can be supposed that there are still one or more other substances which cooperate with PPV. The increase of glucose metabolism in the liver in the study might be as an attempt to provide the precursors of milk compounds and/or fulfillment of energy metabolism for increasing the proliferation of lactating mammary gland cells and their synthetic activities [4].

CONCLUSIONS

The influence of the oral administration of SAP suspension 14.17 % (PPV dose equivalent to 2 mg/kg body weight, 0.95±0.14 ml per animal) and PPV-hydrochloride solution 0.5 % (2 mg PPV/kg body weight, 0.78±0.21 ml per animal) on the White New Zealand Rabbits twice a day
showed an increase the glucose absorption in the gastrointestinal after 15th days of applications. It could be seen that glucose concentration in the portal vein enhanced significantly at this time. The administration of SAP and PPV caused a surplus of glucose in the liver, it were presented by the positive flux of glucose in the liver obtained after 15th days of applications. Especially the administration of SAP caused a surplus of glucose obtained earlier and to a higher extent than after PPV administration. As a consequence of the surplus of glucose in the liver, probably the activity of glycogenesis, lipogenesis, and/or synthesis of amino acids was increased by PPV and SAP administration. Besides, the energy metabolism of parenchyma cells might be enhanced as well. The PPV content of the SA leaves might be plays an important role in the effects of SA leaves. It is still conceivable that one or more substances cooperate with PPV.

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