



Analysis of Medicinal Plants on Embryo Development of Mice (*Mus musculus* L.) And White Rats (*Rattus novergicus*): A Systematic Review

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Abstract

White rats are often used to assess protein quality, toxicity, carcinogenic, and pesticide content of an agricultural food product. *M. Musculus* mice are rodents that are very easy to breed, and easy to maintain. Embryogenesis is the process of growth and development of the embryo. The purpose of this study was to analyze medicinal plants on the embryonic development of Mice (*Mus musculus* L) and White Rats (*Rattus Novergicus*). This method uses a Systematic Review approach which is based on the Preferred Guide to Reporting Items for Systematic Review and Meta-analysis (PRISMA). Total of 700 articles were obtained which then entered the elimination stage resulting in 50 articles on medicinal plants (*Mus musculus* L) and White Rats (*Rattus Novergicus*). Based on the results of the study, it can be concluded that the identification of medicinal plants that are toxic to the embryonic development of Mice White Rats (*Rattus Novergicus*).

Keywords: Ecosystem Health, Embryo of white rats, Extracts of Ajwa Dates, Resource Recycling.

Abstrak

Tikus putih sering digunakan untuk menilai kualitas protein, toksisitas, karsinogenik, dan kandungan pestisida dari suatu produk pangan pertanian. Mencit *M. musculus* merupakan hewan pengerat yang sangat mudah berkembang biak, serta mudah dipelihara. Embriogenesis adalah proses pertumbuhan dan perkembangan embrio. Tujuan dari penelitian ini adalah menganalisis tumbuhan berkhasiat obat terhadap perkembangan embrio Mencit (*Mus musculus* L) dan Tikus Putih (*Rattus Novergicus*). Metode ini menggunakan pendekatan Systematic Review yang didasarkan pada Preferred Guide to Reporting Items for Systematic Review and Meta-analysis (PRISMA). Didapatkan sebanyak 700 artikel yang kemudian memasuki tahap eliminasi sehingga diperoleh 50 artikel tentang tanaman obat (*Mus musculus* L) dan Tikus Putih (*Rattus Novergicus*). Berdasarkan hasil penelitian dapat disimpulkan bahwa identifikasi tumbuhan obat yang bersifat toksik terhadap perkembangan embrio Mencit Tikus Putih (*Rattus Novergicus*).

Kata kunci: Ekstrak kurma Ajwa, embrio tikus putih, kesehatan ekosistem, daur ulang sampah

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INTRODUCTION

In Indonesia, there are no less than 2039 species of medicinal plants originating from tropical forests ¹. This situation makes Indonesia superior as one of the world's important biodiversity warehouses for pharmaceutical ingredients or drugs for human health ². Testing of medicinal substances intended for use in humans needs to be investigated by including human subjects as the final test tube. Human volunteers are ethically allowed to be included in the material to be tested has passed thorough laboratory testing, followed by using experimental animals for feasibility and safety.

Various small animals have certain characteristics that are relatively similar to humans, while other animals have similarities with the physiological aspects of human metabolism. White rats are often used to assess protein quality, toxicity, carcinogenic, and pesticide content of an agricultural food product³. *M. Musculus* mice are rodents that are very easy to breed, and easy to maintain. This is very advantageous in experimentation/research because mice can breed throughout the year. The mouse is one of the few mammalian species whose genome sequence can be determined and technically does not undergo genetic changes from each generation of development. So that

mice can be categorized conditionally as experimental animals ⁴.

Embryogenesis is the process of growth and development of the embryo. The developmental stage of mammals (including humans) begins with the event of fertilization, namely the meeting/fusion of sperm cells with ovum cells. This fertilization will then produce a new individual cell called the zygote and will carry out growth and development towards the embryo. Organogenesis is the process of forming organs in living things (humans and animals) ⁵. The stages of embryogenesis and organogenesis in their development are always in line, one of which is the development of the organs of the body. Teratogenesis is the formation of congenital defects or abnormal embryonic development, and these abnormalities are a major cause of morbidity and mortality in newborns. This happens because of chemicals, ionizing radiation, viruses, and nutritional deficiencies ⁶. The purpose of this study was to analyze medicinal plants on the embryonic development of Mice (*Mus musculus* L.) and White Rats (*Rattus Novergicus*).

METHODOLOGY

This review uses a Systematic Review that was carried out in August-September 2022, in several databases, namely Pubmed, Sciencedirect, NCBI, and Elsevier with an article publication time span of 1973-2022 ⁷. The inclusion



criteria consisted of articles reporting “medicinal plants, embryos, mice (*Mus musculus* L.) and white mice (*Rattus Novergicus*)”. Based on the results of the search carried out which then entered

the elimination stage, there were 50 articles that were then included in the review results of this manuscript, according to the study by ⁸.

RESULT AND DISCUSSION

Table 1. The number of embryos and the percentage of morula and blastocyst in mice given red fruit extract (EBM) (Eriani).

Treatment	Number of embryos	Morula and blastocyst percentage	
		Morula	Blastosis
red fruit extract 0 ml	105	6,63±1,28a	93,36±1,28a
red fruit extract 0.05 ml	105	15,88±3,37b	84,12±3,37b
red fruit extract 0.1 ml	105	28,47±2,46c	71,53±2,46c

Note: different superscripts in the same column show significantly different (P<0.05).

Table 2. Number of embryos in mice given Pandanus conoideus var. yellow fruit (Muna L, Astirin OP, Sugiyarto. 2011)

Parameter		Dosage (mL)				
		Control	0,02	0,04	0,08	0,16
Number of 5 pregnant women	5	5	5	5	5	5
	58	52	44	46	44	44

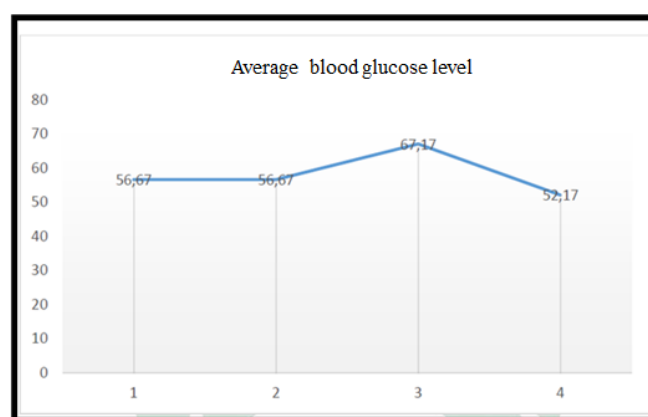


Figure 1. Average blood glucose levels in Mice Embryo after administration of ajwa date palm pulp extract (*Phoenix dactylifera* L.) (Setyaningsih N, 2018)



Development of Mice Embryos Given Red Fruit Extract

Giving red fruit extract resulted in delays in embryo development until the blastocyst stage. The decline in the developmental ability of mammalian embryos is due to mitochondrial dysfunction and low available ATP. According to Silva (2006), during embryonic development, metabolism in cells forms ROS in their extracellular surroundings⁹. The effects of ROS on embryonic development can block or retard normal development in embryos. The more cells the embryo develops, the more ROS are formed. After fertilization at the beginning of embryonic development, the embryo is still dependent on gene expression from the mother, so it can still counteract ROS with the help of GSH from the mother. The embryonic genome in cows is activated at the 8-16 cell stage, without the synthesis of GSH from the mother's body¹⁰. The embryonic genome in mice is activated at the 2-cell stage. In the absence of gene expression from the mother in the embryo to counteract ROS, the embryo requires an increase in ATP for development. Oxidative stress has implications for various cell damage including lipid peroxidation layer, amino acid oxidation, apoptosis and necrosis which will reduce the success of in vitro embryo production¹¹¹².

The decrease in the ability of embryo development to the blastocyst stage in this study, may also be caused by the administration of red fruit extract for a long time (7 days before fertilization and continued 3 days after fertilization) which resulted in damage to uterine organs. Red Fruit extract can cause degeneration and congestion of the uterine organs. Congestion is a condition caused by disruption of blood flow, so that blood circulation becomes slow and oxygenation to tissues decreases because blood is still in the blood vessels. This event can reduce the supply of oxygen in the uterine fluid, while the preimplantation embryo is very dependent on the secretions of the oviduct and uterine glands. Embryo development is an activity under aerobic conditions, namely activities that require oxygen¹³. Embryo development will be hampered by reduced oxygen supply due to uterine congestion.

Another thing that can reduce the ability of egg cells to develop to the blastocyst stage in vivo in mice is because Red Fruit (*Buah Merah*) extract also functions as an anticancer or inhibits cell development. Furthermore, anticancer substances can interfere with microtubule activity. Disruption of the spindle microtubules can interfere with the activity of dividing cells. Red fruit extract which



has been shown to have anticancer and antitumor activity, can also interfere with the formation of microtubule spindles which may contribute to the decrease in the ability of egg cells to develop to the blastocyst stage ¹⁴.

Pandanus conoideus var. yellow fruit against white mouse embryos (Rattus Novergicus)

Pandanus conoideus var. Yellow fruit is an alternative medicine to treat cancer ¹⁵. This anti-cancer drug is used by all cancer patients, including pregnant women, while pregnant women are very susceptible to drugs, especially during organogenesis ¹⁶. Anti-cancer drugs are teratogenic; not only affects cancer cells, but can affect normal cells in the vicinity¹⁷¹⁸. Fetal tissue grows at high speed, its cells divide rapidly so it is very susceptible to anti-cancer drugs. In addition, the drugs consumed by the mother will pass to the fetus through the placenta, namely through the same route that is passed by the nutrients needed for fetal growth and development. Drugs that reach the fetus can cause miscarriage, malformations or even death of the fetus ¹⁹.

PKH states that fat consumption can affect the production of progesterone. This is because the number of embryos in the uterus also affects the availability of space for embryo development and blood

supply²⁰. It is known that the fewer the number of implantations in the uterus, the availability of nutrients for the fetus will be fulfilled, so that the weight of the fetus with its nutrition will increase.

Provision of Ajwa Dates Flesh Extract (Phoenix dactylifera L.) Against Blood Glucose Levels of Mice Embryo (Mus musculus)

Annisafitria explained that dates are also believed to be good antioxidants. Not only as antioxidants, dates can also be anti-microbial, anti-mutagenic, anti-inflammatory, and anti-diabetic²¹. Rahmani et al. (2014) stated that ajwa dates can cure various types of diseases that play a protective role in liver toxicity so that the body's metabolism remains balanced²². This protective benefit is due to the fact that Ajwa dates contain several active compounds that are beneficial to the body such as tannins, saponins, flavonoids, polyphenol alkaloids and so on. Polyphenols in ajwa dates have the highest concentration compared to other types of dates²³²⁴²⁵. Saryono stated that dates can prevent anemia, help the involution process and improve milk quality. Ajwa dates are also useful for fetal development and growth²⁶. Suroso's research states that there is an effect between regular consumption of date palm juice at the end of pregnancy and the amount of labor bleeding. Ajwa dates are also beneficial for the



development of the embryo²⁷. The content in it can increase embryo immunity, prevent anemia, improve digestion and help growth²⁸. The administration of ajwa date fruit extract on the blood glucose levels of mice did not show a significant effect. This is due to the presence of fructose in ajwa dates which can significantly suppress the increase in blood glucose levels.

Fructose enters the cell with the help of GLUT-5. GLUT-5 functions to transfer fructose into cells. The action of GLUT-5 is independent of the presence of insulin. Fructose has a simpler structure than glucose so it is easier to enter cells. After that, glucose, galactose and fructose that have been absorbed in the intestinal cells diffuse into the blood through GLUT-2. Fructose can be consumed by diabetics because the transport of fructose to the body's cells does not require insulin, so it does not affect insulin secretion. In addition, the excess of fructose is 2.5 times as sweet as glucose²⁹. Although there is no increase in blood glucose levels in the embryo, it does not mean there is no difference at all. There was a difference between the administration groups but it was not significant.

There was an increase in blood glucose levels at several doses when compared to blood glucose levels in the control group. The group that experienced an increase was the P5 group, which was 67.17 mg/dL.

Meanwhile, the P3 group had the same mean value as the mean blood glucose level in the PK group, which was 56.67 mg/dL. However, in the P7 group, glucose levels decreased from all treatment groups, namely 52.17 mg/dL. This is because the content of ajwa date fruit extract contains various kinds of active compounds that are useful for the body. Dates contain carbohydrates, glucose, fructose, sucrose, magnesium, potassium, phosphorus, phosphate, protein, calcium, salicylic acid and several vitamins and a high content of polyphenols which are useful as antidiabetic, anti-inflammatory and good for fetal growth and development^{21,26}.

The increase in blood glucose levels in the P5 group was thought to be due to fructose. Fructose has a low glycemic index. Carbohydrates that have a low glycemic index trigger a slight increase in blood glucose levels, while those with a high glycemic index trigger high blood glucose levels as well. The increase in blood glucose levels in the P5 group did not exceed the blood glucose levels of normal mice. Normal mice blood glucose levels are 55-175 mg/dL.

This is also due to the influence of estrogen and progesterone. In normal pregnancy, pregnancy is said to be a diabetogenic condition, where the need for glucose will increase. Maternal metabolism undergoes changes for an



adequate and constant supply of glucose for the developing fetus. Maternal glucose is transferred to the fetus by a process of facilitated diffusion. Maternal insulin cannot cross the fetal placenta. At ten weeks' gestation, the fetus can secrete high amounts of its own insulin, allowing the use of glucose obtained from the mother. In the first trimester of pregnancy, maternal glucose levels drop rapidly below normal glucose levels of between 55 and 65 mg/dl. This happens because of the influence of the hormones estrogen and progesterone, so that the pancreas increases insulin production and increases the use of glucose. At the same time, the use of glucose by the fetus increases, thereby lowering maternal glucose levels. In addition, the first trimester is also marked by nausea, vomiting, and decreased food intake so that maternal glucose levels decrease and during the second and third trimesters there is an increase in levels of human placental lactogen, estrogen, progesterone, cortisol, prolactin, and insulin which causes increased insulin resistance. Insulin resistance is a glucose saving mechanism and ensures an adequate glucose supply for the fetus³⁰.

Another mechanism of increased blood glucose levels in the fetus is caused by the influence of the hormone progesterone. Progesterone

can increase insulin secretion, increase fasting blood glucose levels, but decrease insulin effectiveness in peripheral tissues. Cortisol can inhibit the absorption and oxidation of glucose, increase the formation of glucose by the liver and can increase the secretion of glucagon. Thus, in the last trimester, fasting can lead to mobilization of maternal triglyceride stores causing maternal fatty acid levels to increase dramatically. This fatty acid is an alternative substrate for maternal metabolism so that glucose can be used for the brain and meet the needs of the fetus. As glucose uptake by tissues is suppressed, glucose levels increase which leads to stimulation of insulin secretion from the pancreas because hyperinsulinemia.

Hyperinsulinemia is a normal development in late pregnancy because insulin levels double in the third trimester³¹. In the P7 group, there was a decrease in blood glucose levels. This is because the consumption of fructose in the mother mice is too much. Fructose can have a hypoglycemic effect and fructose also has a low glycemic index so that its consumption in large quantities can reduce blood glucose levels³².

Ajwa dates contain much higher levels of fructose compared to other dates, ie per fruit has a fructose content of 48.7 grams³³ and is safe for consumption if the levels are 25-40



grams per day ³⁴. When symptoms arising from mild hypoglycemia are manifested by blood glucose levels 55 mg/dL³⁵. The mechanism of hypoglycemic activity is thought to be due to the presence of flavonoid glycoside compounds. The hypoglycemic mechanism is thought to be caused by flavonoid glycoside compounds that are absorbed in the blood and increase the solubility of blood glucose so that it is easy to be excreted through urine ³⁶. Another hypoglycemic mechanism is the ability of quercetin which is a type of flavonoid in inhibiting GLUT 2 of the intestinal mucosa so that it can reduce glucose absorption. This causes a reduction in the absorption of glucose and fructose from the intestine so that blood glucose levels fall. GLUT 2 is suspected. It is the major glucose transporter in the intestine under normal conditions. In a study conducted by Songit was found that flavonoids can inhibit glucose absorption ³⁷. When quercetin is ingested with glucose, hyperglycemia is significantly decreased. This shows that quercetin can inhibit glucose absorption through GLUT 2 ³⁷.

The decrease in blood glucose in mice was also caused by the presence of xanthone compounds which are flavonoid compounds. Xanthenes are antioxidant compounds ³⁸. This compound studied in mangosteen rind

extract can neutralize free radicals and can help lower blood sugar levels and overcome fatigue caused by unbalanced blood sugar levels ³⁹.

Polyphenols are antioxidant compounds. Ajwa dates have a very high polyphenol content. Polyphenols are compounds that have activity as antioxidants. It is known that antioxidants can lower blood glucose levels. Polyphenolic compounds in ajwa dates that are thought to be able to lower blood glucose levels are polyphenol acid (gallic, protocatechuic, hydroxybenzoic, vanillis, siovanilic, syrigic, caffeic, ferulic, sinapic, pcoumaric, isoferulic), flavonoid glycosides (quercetin, and kaempferol, apigenin) and anthocyanidins ⁴⁰. Giving dates with a dose of 5 grains is considered the right dose to be given to pregnant mice, because at that dose glucose levels are high blood increased slightly. While at a dose of 7 grains, there was a decrease because the polyphenol content in Ajwa dates was too high so that the antioxidant activity was greater and resulted in indications of mild symptoms of hypoglycemia in mouse embryos ⁴¹.

In addition to fructose, another possibility that can lower blood glucose levels is flavonoids. Flavonoids are able to reduce oxidative stress and reduce ROS (Reactive Oxygen Species) which have a protective effect on pancreatic beta cells and increase insulin



sensitivity. Flavonoid compounds, especially quercetin, are inhibitors of GLUT 2 in the intestinal mucosa, a pathway for glucose and fructose absorption in the intestinal membrane⁴². This mechanism is non-competitive, causing a reduction in the absorption of glucose and fructose from the intestine so that blood glucose levels fall⁴³.

Flavonoids have a mechanism in inhibiting phosphodiesterase so that cAMP levels in pancreatic beta cells increase. This stimulates insulin secretion via the Ca pathway. Increased levels of cAMP will cause the closure of K⁺ ATP channels in the plasma membrane of beta cells. This situation results in membrane depolarization and the opening of voltage-dependent Ca channels thereby accelerating the entry of Ca ions into the cell. This increase in Ca ions in the cytoplasm of beta cells will cause insulin secretion by pancreatic beta cells⁴⁴.

CONCLUSION

Based on the results of the search, 50 articles were obtained which were used as analysis material, where it can be concluded that more in-depth research is needed on medicinal plants that are toxic to the embryonic development of Mice (*Mus musculus* L.) and White Rats (*Rattus Novergicus*).

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