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Review

Avocatin B: Its Role in Cancer and Diabetes Mellitus Treatment

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ABSTRACT

Avocado is at the forefront with its fat-soluble compounds and the phytochemicals it contains, and its health benefits. The odd-numbered carbon lipid, avocatin B (AvoB), obtained from avocado, emerges as an alternative therapeutic approach in epidemic diseases such as cancer and diabetes, with various mitochondrial-focused mechanisms. Avocatin B plays a regulatory role against fatty acid oxidation, transcription factor 4, and free radicals, which are the basis of these diseases. With its functions of lowering blood sugar and increasing insulin sensitivity, AvoB has been shown to have curative effects on diabetes. Since there are limited studies in the literature, it is not clear how to use AvoB routinely. However, it has the potential to be used as an alternative method in the treatment of diseases such as diabetes and cancer in the future. This review aimed to assess the effectiveness of AvoB, a compound identified as having anti-acute myeloid leukemia properties, and investigate the pathways associated with its effects on obesity and diabetes, both of which are diet-related diseases.

Keywords: Acute myeloid leukemia, avocado, avocatin B, cancer, diabetes mellitus, fatty acid oxidant

Food and dietary components are important elements in health and disease. The severity of the global obesity and cancer epidemic has increased significantly in recent years.[1-4] Diet-induced obesity (DIO) is a major risk factor associated with metabolic complications such as insulin resistance, type 2 diabetes mellitus (T2DM), and cardiovascular diseases.[5-7] Metabolic dysfunction caused by lipotoxicity, ie free fatty acid, is being investigated. It has been shown that the pathways related to fuel oxidation of tissues are significantly impaired in obese and diabetic patients.[8,9] There are theories that insulin resistance is mediated by fatty acid oxidation (FAO).[10,11] The associations between triglyceride accumulation in skeletal muscles, FAO, and glucose oxidation are thought to be associated with insulin resistance as well as fatty acid uptake.[12] In addition, utilizing fatty acid metabolism to improve DIO and lipotoxicity-related metabolic complications is on the agenda. Although actively validated small molecules affecting this pathway are not yet available, they are being tested. Avocatin B (AvoB), a lipid derived from avocado, has been shown to be an inhibitor of FAO, which accumulates in mitochondria to induce leukemia cell apoptosis without toxicity to normal cells.[13]

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Food-derived bioactive molecules have shown promise as inventive anticancer agents by targeting leukemia cell metabolism. Therefore, the development of functional foods has increased the number of studies on potential dietary or herbal products, both to identify them and to see their mode of action at the molecular level. Avocado is considered one of the most nutritious commercial fruits and is widely consumed worldwide.[14] It has been shown antioxidant, analgesic, anti-inflammatory, hypocholesterolemic, and anti-cancer effects.[15-20] The anticancer activities of avocados have been associated with more than 20 groups of bioactive compounds, including long-chain lipid molecules such as long-chain fatty acids and their derivatives (avocatins, pahuatins, persenins, and polyhydroxylated fatty alcohols).[21-24] Avocatin B is an odd-numbered carbon lipid with a 1:1 ratio of two 17-carbon lipids produced from avocado fruit

and recently identified as a novel anti-acute myeloid leukemia (AML) compound.[13] However, AvoB was found to inhibit FAO and improve insulin sensitivity as well as glucose tolerance in DIO mice. Studies are underway on whether AvoB can improve the effects of lipotoxicity in skeletal muscle and pancreatic tissue *in vitro* and *in vivo*.[25] This review investigated the efficacy of AvoB, as well as the pathways associated with its identification as an anti-AML compound and its effect on diet-related diseases such as obesity and diabetes. Avocatin B, which is observed as a promising compound despite limited studies in the literature, has been presented to the food sector as a powder and capsule since 2012 with the aim of serum glucose regulation and healthy metabolism.

AVOCADO

Avocado is botanically known by the name *Persea americana* Mill. A tropical and subtropical fruit native to Mexico and Central America, the avocado is of high and growing interest globally. The healthy nutritional benefits significantly increase the marketing and distribution opportunities. In the Lauraceae family, avocado is the only fruit that is consumable and of high value. It is also very valuable from a commercial point of view. Avocado in the Lauraceae family; is the only fruit that has the highest value and can be consumed. It is also very valuable from a commercial point of view. Mexico is the main producer and exporter of avocados, with more than 30% of the world's avocado production.[26] The earliest archaeological evidence for avocado seeds is from Coxcatlan Cave in Mexico.[27] Avocado is often called alligator pear, vegetable butter, or sometimes butter pear, due to its shape and soft texture. The sizes of avocados vary from 120 g to 2.5 kg. They may have a rough or smooth surface and thin or thick shells.[28] The species are grouped as A or B type according to the type of flowering and the flowers are functionally female or male.[29] The ripening of avocados is quite distinctive compared to other fruits since ripening occurs after it is harvested, not while it is on the tree. Avocados on trees can remain unharvested for months.[30,31]

There are many avocado species with different shapes, tastes, textures, colors, and odors according to the climate of the growing region. The commonly known and commercially used varieties are 'Hass' and 'Fuerte'.[29] Avocado is a fruit rich in nutritional value. Its fat-soluble compounds and various phytochemicals are considered to be beneficial for health.[32] It has been reported that the nutritional composition of avocado pulp has moisture content ranging from 67-78%, fat content ranging from 12-24%, carbohydrate content ranging from 0.8-4.8%, and protein content ranging from 1.0-3.0%. Avocados have energy ranging from 140-228 kcal.[33-35] High-fat content compared to other fruits, richness in glycolipids, and phospholipids are among the most important factors in avocados. It contains monounsaturated fatty acids that increase blood levels of beneficial high-density lipoprotein (HDL) while reducing blood levels of unwanted low-density lipoprotein (LDL).[27,33,36] Compared to other vegetable oils, avocado oil is known to contain high levels of monounsaturated fatty acids (oleic and palmitoleic acids), low amounts of polyunsaturated fatty acids (linoleic acid), and significant amounts of saturated fatty acids (palmitic and stearic acids).[34] Other fatty acids such as myristic, linolenic, and eicosenoic acids are also present in small amounts in avocado oils.[37] It has been found that these fatty acids vary depending on the amount, content and distribution, varieties, maturity stage, anatomical region of the fruit, and geographical location where it grows.[38,39] Avocados contain large amounts of potassium, phosphorus, magnesium, calcium, sodium, and other minerals, including iron and zinc, in amounts less than 1 mg per gram of fresh avocado weight.[27,36] Recently, avocado production and export have been increasing due to the increasing interest in this fruit in the food-related and medicinal fields due to the above-mentioned properties.[40,41]

AVOCATIN B

Avocatin B is an odd-numbered carbon lipid with a 1:1 ratio of two 17-carbon lipids, as shown in Figure 1, identified as an anti-AML compound in AML.[42] Odd-numbered carbons are rare, cannot be produced endogenously, and can only be obtained from dietary sources. Adipose tissue can exhibit consistent fat deposition by accumulating only one-carbon fatty acids.[43-45] In humans, 13, 15, and 17 carbon-long lipids are used as serum and adipose tissue biomarkers for dietary fat intake since these fatty acids are more slowly catabolized than even-numbered fatty acids.[46,47] In conclusion, AvoB is a new compound with cytotoxic activity and inhibits FAO. Many studies have been conducted to confirm the antimicrobial activity of avocados.[48] Ethanol extracts of avocado seed showed protective activity against bacteria in determined Gram-positive and Gram-negative bacteria.[49] AvoB, the stress-induced transcription factor, has been found to mediate activating transcription factor 4 (ATF4), 5'adenosine monophosphate-activated protein kinase (AMPK) signaling, and reactive oxygen

species (ROS) regulation.[42] Mechanistically, AvoB has been observed to accumulate in mitochondria to suppress FAO.[50] No dose-limiting toxicity was found in a phase 1 study of a randomized, double-blind, placebo study of humans consuming 50 or 200 mg of AvoB. Mice induced by a high-fat diet were administered oral AvoB twice weekly for five weeks. AvoB has been observed to increase glucose tolerance, glucose utilization, and insulin sensitivity by suppressing FAO.[25] Avocado-derived AvoB compound has potential clinical utility. More pharmacokinetic studies are needed as therapeutic agents.

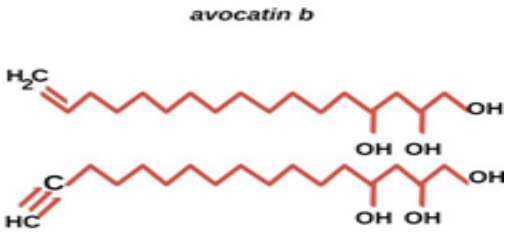

Figure 1. The chemical structure of avocatin B, an odd-numbered carbon lipid derived from the avocado fruit, contains two 17-carbon lipids in a 1:1 ratio.

CANCER AND AVOCATIN B

Cancer causes more deaths than known acquired immunodeficiency syndrome, diabetes, tuberculosis, and malaria.[51] The disadvantages of anticancer regimens include the complex mutational picture of cancer, late diagnoses, expensive therapeutic alternatives, and resistance to chemo and radiation therapies. Chemotherapy-related side effects and toxicity are one of the most difficult aspects of cancer treatment.[52-54] In the 1981–2010 timeframe, nearly half of the Food and Drug Administration-approved anti-cancer drugs consisted of natural products or derivatives.[55] Therefore, the search for safer options, which can be the sole or additional treatment with standard drugs, is becoming a priority in anticancer research.[56] The *in vitro* cytotoxic properties of avocado against different cancer cell lines such as breast, colon, liver, lungs, larynx, leukemia, esophagus, mouth, ovary, and prostate have been extensively reported in the literature.[57-64] As a result of the studies, he discovered the benefits of not only the pulp, which is the edible part of the avocado, but also the leaves, peel, and seeds. The chemical profiles of different parts of avocado vary between cultivars, so bioactivities may vary.[65] Researchers found that ethanol extracts of avocado endocarp, seeds, and leaves activate transcription factor p53, caspase-3, apoptosis-inducing factor, and oxidative stress-induced apoptosis in Jurkat lymphoblastic leukemia cells via mitochondrial membrane depolarization.[66,67] Acetone extract of avocado pulp rich in lutein, zeaxanthin, beta (β)-cryptoxanthin, alpha (α)-carotene, β-carotene, α-tocopherol, and gamma (γ)-tocopherol has been shown to inhibit PC-3 prostate cancer cells in the G2/M phase.[59] According to data from various studies, consumption of ≥1 serving of avocado per week was associated with reduced total risk.[68] AvoB, a lipid-derived agent from the avocado fruit, has recently been identified as a potential therapeutic that selectively targets cancer stem cells (CSC) of AML.[69] In fact, the anti-CSC effects of AvoB are based on mitochondria. It is mediated by the inhibition of FAO, which leads to a decrease in nicotinamide adenine dinucleotide phosphate (NADPH) levels and induces ROS-dependent apoptosis.[70,71] In addition, a synergistic anticancer effect between AvoB and standard chemotherapeutics has been observed in AML.[72] As noted above, FAO has been implicated in the CSC self-renewal of several tumor types. Therefore, the combination of pharmacological inhibition of mitochondrial FAO together with conventional anti-cancer drugs could potentially have an improved therapeutic effect among a wide range of cancers. Fatty acid metabolism varies in cancer cells.[73] Recently, interest in lipid metabolism inhibitors, especially FAO as new treatments, has increased. Avocatine B has also been tested as a new therapeutic in leukemia cells.[13] Potentially, through competitive inhibition of fatty acids, it prevents FAO from accumulating in mitochondria and increases the accumulation of ROS that trigger apoptosis.[72] A more comprehensive understanding of the roles of short and medium-chain fatty acids, L-carnitines, and FAO in cancer survival is essential to develop effective combination therapies.

DIABETES AND AVOCATIN B

Glucose regulation in the blood is provided with the help of β-cells secreted by the pancreas. Since insulin is the only hormone that can lower blood glucose, it is an important regulator of homeostasis. As a result of the degeneration of β-cell function, high glucose in the blood leads to diabetes mellitus. It occurs due to the destruction of the β-cells of the pancreas, which is responsible for secreting insulin, or the destruction of its function. It is a metabolic disorder that has become a pandemic. According to

predicted studies, it is estimated to reach 552 million in 2030.[74,75] There are two basic types, T1DM and T2DM. While T1DM is characterized by β-cell destruction resulting in impaired autoimmune function, the pathogenesis of T2DM causes β-cell dysfunction with a combination of genetic and environmental factors, followed by the development of resistance in insulin target tissues.[76] Monogenic diabetes, a less common version of the disease, is associated with specific gene mutations related to pancreatic development and β-cell function.[77,78] The existence of various therapeutic approaches for diabetes management is seen in the literature. Dietary control, oral antidiabetic agents, and insulin are the most commonly used methods.[79–82] Natural products with antidiabetic properties can be an alternative to treat diabetes with minimal side effects. Avocado seed helps treat T2DM by targeting peroxisome proliferator-activated receptor-gamma in the same way as an antidiabetic drug (thiazolidinediones).[83]

Avocado seeds added to a high-sugar diet were given to hypertensive rats, showing antidiabetic and lipid-lowering effects by lowering blood sugar and cholesterol. The blood glucose lowering effect was attributed to bioactive compounds that aid in the storage of glucose to glycogen in liver cells.[84] In alloxan-induced diabetic rats, 300 or 600 mg/kg body weight avocado seed extract treatment was found to repair damage to pancreatic islet cells by lowering glycemia.[85] Avocatin B has also been found to suppress FAO and improve glucose tolerance as well as insulin sensitivity in DIO mice. It strongly confirms the inhibitory effect of AvoB treatment on FAO *in vitro*. To evaluate the pharmacokinetics of AvoB in humans and to confirm its safety, a randomized, double-blind, placebo-controlled clinical trial was conducted with 30 healthy volunteers at low (50 mg) and high doses (200 mg). Daily AvoB swallowed for 60 days. According to observations, AvoB was well tolerated, with minor gastrointestinal effects also noted in the placebo group. The weight loss trend measured in both AvoB-supplemented groups between baseline and day 30 was not statistically significant. AvoB, derived entirely from avocado, is an interesting compound for metabolic disorders such as obesity-associated insulin resistance, and diabetes.[25]

In conclusion, therapeutic treatment methods against diabetes and cancer diseases that have become pandemics are still being sought. Since the side effects of cancer treatment methods are staggering, natural interventions gain importance. Therapeutic alternatives for diabetes, which has become an epidemic disease despite the discovery of insulin, are also of interest. In our article, we discussed the two 17-carbon lipid-containing avocado fruit of avocado fruit, which has become popular all over the world in terms of health. Avocatin B is one of the most interesting food compounds of recent times. It was defined as an anti-AML compound after it was seen that it showed therapeutic effects by targeting cancer cells in AML. The possible mechanism of AvoB appears to be mitochondrial-focused. It is thought that problems occur in the pathways related to fuel oxidation of tissues in these diseases. AvoB, which accumulates in the mitochondria to suppress FAO, lowers NADPH levels and offers its antidiabetic and anticancer effects. It has been suggested to inhibit FAO in skeletal muscle and pancreatic β-cells in diabetes, reverse insulin resistance, and restore glucose tolerance in DIO. It has been seen that there are very limited studies in the literature on this lipid compound, which offers therapeutic effects in various aspects. Although oral supplements containing AvoB are on the market, it is clear that more pharmacokinetic and other studies are needed on how it can be used in the routine.

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