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Evolution of research in the Pharmacology Laboratory at the Universidad Autónoma Metropolitana-Iztapalapa: A Historical Review

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Abstract. This paper aims to trace essential milestones in the history of the investigation activities developed throughout the past four decades in the Laboratory of Pharmacology of the Universidad Autónoma Metropolitana Iztapalapa (LFUAMI), emphasizing the contribution of Dr. Rubén Román-Ramos, the leader who guided and promoted the chemical and pharmacological investigation of natural products in the LFUAMI. Dr. Rubén Román-Ramos impacted the development of new generations, who continue contributing to and strengthening this field, both outside and inside our university, by developing the science and technology in chemistry and pharmacology research. From this historical review of the LFUAMI, it is possible to identify leading features in its different periods; the periods are characterized by the scientific evidence primary generated, the methodological impact in the results, and technological development and impact in the state of the art. It should be noted that the periods overlap, creating a cumulative effect. To conclude, we will summarize the historical milestones and present some research avenues currently pursued and some perspectives.
Keywords: Medicinal plants; anti-diabetic plants; hypoglycemic plants; phytochemistry; pharmacology.

Resumen. Este artículo es una revisión acerca de la investigación desarrollada durante los últimos 40 años en el Laboratorio de Farmacología de la Universidad Autónoma Metropolitana Iztapalapa (LFUAMI), enfatizando la contribución del Dr. Rubén Román Ramos, profesor quien guió y promovió la investigación químico-farmacológica de este laboratorio, impactando en la formación de nuevas generaciones de investigadores, quienes continúan su legado en la investigación de productos naturales, fortaleciéndolo, tanto dentro como fuera de nuestra universidad. A través de esta revisión histórica fue posible identificar algunas de las características sobresalientes de cada periodo del LFUAMI en las últimas cuatro décadas, destacando la calidad de la evidencia científica generada, la influencia metodológica y el desarrollo tecnológico de los distintos estudios, así como su impacto en el estado del arte. Para concluir, se resumen algunos de los desarrollos más relevantes, se presentan algunas de los trabajos recientes y las perspectivas de investigación más importantes de este consolidado grupo de trabajo.
Palabras clave: Plantas medicinales; plantas antidiabéticas; plantas hipoglucemiantes; fitoquímica; farmacología.

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Introduction

This paper offers a concise historical review of the systematic research conducted in the pharmacology laboratory of the Universidad Autónoma Metropolitana Iztapalapa (LFUAMI) over the past four decades, highlighting its evolution and contributions to biomedical sciences. The paper comprises four parts. The first one explores the origin and essential characteristics of the laboratory, spanning from its establishment in 1986 to the year 2000. The second part presents the three main periods of the laboratory's evolution: The foundation, the strengthening, and the diversification periods, covering the years 2001 to 2010. The third part explores the technological period, spanning from 2011 onwards. These periods are characterized by distinct features, including scientific evidence, methodological diversity, and technological development. The last part of the paper summarizes the main elements of the laboratory's history and presents future research directions.

Foundation period by Professor Ruben Roman-Ramos (1986-2000)

The establishment of the LFUAMI was influenced by a global surge of interest in the study of medicinal plants, particularly evident in Mexico during the late 1970s. This period coincided with the creation of the Mexican Institute for the Study of Medicinal Plants (IMEPLAM), reflecting a growing recognition of the potential therapeutic benefits of natural substances. In Mexico, researchers and institutions alike were drawn to the study of medicinal plants, driven by a desire to explore traditional healing practices and uncover potential new sources of pharmacological agents.

Dr. Rubén Román-Ramos (Fig. 1), a University of Peoples Friendship graduate in Moscow, Russia, obtained a bachelor's and doctoral degree in medicine, specializing in Endocrinology. He began his illustrious research career at the IMEPLAM under the mentorship of Dr. Xavier Lozoya Legarreta, then the institute's director. At IMEPLAM, Dr. Román-Ramos embarked on groundbreaking research focused on the therapeutic potential of indigenous Mexican plants for managing diabetes mellitus. Utilizing his expertise in endocrinology and experimental medicine, he implemented an innovative experimental model involving pancreatectomized rabbits. This model enabled him to systematically study the potential efficacy of traditional medicinal plants, including *Tecoma stans* ("tronadora"), *Cecropia obtusifolia* ("guarumo"), and *Opuntia streptacantha* ("nopal"), in controlling diabetes mellitus [1-3]. Dr. Román's pioneering work in this area established him as a trailblazer in ethnopharmacology and positioned him as a leading authority on the anti-diabetic properties of Mexican flora. His research laid the groundwork for subsequent investigations into the therapeutic potential of natural remedies for managing diabetes mellitus, contributing significantly to our understanding of traditional medicine practices in Mexico.

Fig.1. Dr. Rubén Román-Ramos.

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The LFUAMI was founded in 1986 by Dr. Rubén Román Ramos to make progress in research and education in pharmacology and chemistry. This idea created a space dedicated to interdisciplinary pharmacological research to provide students and teachers access to state-of-the-art facilities and resources, contributing their experience to developing academic programs and research initiatives within the university. From his ingress in 1986 until 2023, Dr. Roman served as the head of the LFUAMI, and all that time, offered technical consultancy in the areas related to drug activity, natural products, and diabetes mellitus, beginning to undertake sponsored research projects as per norms of the UAM. Under the leadership of Dr. Román-Ramos, the LFUAMI quickly became a hub of scientific inquiry and innovation. Through collaborative research projects and educational programs, the laboratory played a pivotal role in advancing knowledge and understanding of pharmacology within the university community and beyond, integrating medical, biological, and chemical perspectives, and reflecting an avant-garde vision in the field.

In addition to the plants previously mentioned, Dr. Roman-Ramos conducted research on the effects of *Garcinia cambogia* ("garcinia") and other compounds and pharmaceutical formulations for obesity [4]. This research included investigations into the first thiazolidinedione, troglitazone (Rezulin), for diabetic patients. However, due to its hepatotoxic effects, troglitazone was ultimately withdrawn from the market. This research led to new thiazolidinediones, such as rosiglitazone and pioglitazone. Dr. Román-Ramos was involved in clinical research on rosiglitazone, contributing to our understanding of its therapeutic effects. [5-6].

As a full-time professor at our university, Dr. Roman-Ramos served in academic and administrative positions, including the Head of Area, Head of Department, Director of Division, and Coordinator of the PhD Programme in Biological Sciences at UAM, among other academic and administrative positions. He holds the prestigious National Researcher Level III title, awarded by the National System of Researchers (SNI) of CONACYT, now CONAHCYT. Dr. Roman-Ramos has significantly contributed to education and research, having imparted over 250 undergraduate and graduate courses. He is also the author of over 140 scientific publications and has participated in over 400 congresses and conferences. In addition to his academic achievements, Dr. Roman-Ramos has shown innovation and entrepreneurship with five patented models. His dedication to his work is evident in the more than 4,500 citations.

Strengthening and diversification period (2001-2020)

In the previous period, the biological assays in vivo, utilizing experimental animals, were mainly designed to determine the hypoglycemic and antihyperglycemic effects from a quantitative perspective. During this period of strengthening and diversification, researchers explored new methods and chemical tools for qualitative and quantitative analysis. A notable emphasis was on advancing in vitro assays, leveraging cellular culture techniques for more detailed assessments. Additionally, researchers utilized extractive methodologies to isolate natural products, facilitating the subsequent processes of compound isolation, purification, and identification by phytochemistry techniques. These approaches not only broadened the scope of research but also enhanced the precision and depth of both qualitative and quantitative analyses. Since its inception, our research group's focus has expanded and evolved under the successful leadership of Dr. Roman-Ramos, who has maintained high levels of academic productivity and facilitated the progression of the original research line. Since 1986, our research has primarily centered on pharmacological studies of medicinal plants for managing diabetes mellitus. Over time, this focus has broadened to encompass plants, other natural sources, and synthetic resources. Furthermore, our research has extended to include other related metabolic pathologies such as obesity, hypertension, and various dysfunctions. This evolution has led to our current research line: Pharmacology and chemistry of substances for treating metabolic syndrome (MS) and other chronic degenerative diseases.

During this period, our primary aim was to conduct high-quality research in the area, focusing on advancing chemical-pharmacological investigations of natural products at a mechanistic level. This endeavor involved the rational design of computer-assisted drugs and the adoption of cutting-edge techniques to elucidate various plants' molecular mechanisms of action. Our goal was to deepen our understanding of these mechanisms and pave the way for innovative approaches to drug development. The results of these investigations have allowed our working group to be recognized as a benchmark in research into natural resources with potential

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usefulness in treating MS-related diseases, both at the national and international levels. The transcendence of this research line resides in the epidemiologic importance of this syndrome worldwide [7,8].

Management of MS typically requires a multifaceted approach, often involving polypharmacy, i.e., the administration of various medications such as anti-obesity agents to address weight management, anti-diabetic drugs to regulate blood sugar levels, hypolipidemic medications to manage lipid abnormalities, antihypertensive drugs to control high blood pressure, and antithrombotic agents to reduce the risk of blood clots, among others. However, the use of multiple medications concurrently can pose challenges, including potential side effects, drug interactions, and complications related to polypharmacy. Therefore, careful consideration and monitoring are essential in optimizing treatment outcomes for individuals with MS [7].

An alternative approach to mitigate the challenges associated with polypharmacy lies in using specific components derived from medicinal plants. These components have demonstrated "multitarget" actions capable of comprehensively addressing the complexities of MS. They affect carbohydrate and lipid metabolism and vascular health and possess anti-inflammatory and antioxidant properties. Moreover, they offer the potential to target the underlying issue at the core of MS, namely insulin resistance [9]. Hence, our current line of research aims to clarify the medicinal properties of various potential medicinal resources, establishing a rational basis for their therapeutic use in the MS. In general, our research group has contributed to the discovery and development of bioactive molecules through their chemical and pharmacological characterization, trying to explain their effects not only at the organism level but also at the cellular and molecular level with a mechanistic approach. Several research questions have emerged regarding the study of these resources:

Do they produce hypoglycemic, antihyperglycemic, antihypertensive, antioxidant, and anti-inflammatory, anti-obesity activities? Do they reduce insulin resistance? Do they act through several molecular targets? Can they have only one pharmacological effect or multiple? What are their action mechanisms, and is their action dose-dependent?

We have devised a comprehensive strategy based on bioassay-guided chemical studies to answer these questions. This strategy encompasses in vitro, in situ, and in vivo biological studies, including acute, subacute, and chronic evaluations of extracts, fractions, or pure compounds isolated and identified through conventional extractive techniques and chromatographic and spectroscopic methods. Parameters measured during these studies include blood glucose levels, plasma insulin, triglyceridemia, cholesterolemia, liver transaminase levels, inflammatory cytokines, oxidant stress markers, and various transcription factors. Different cell lines, such as adipocytes, hepatocytes, skeletal muscle, macrophages, endothelial, pancreatic, and isolated tissues, have been used in vitro. The techniques used in these studies were RT-qPCR, ELISA, epifluorescence, Western Blot, histological analysis, kinetics, and enzyme activity, including the chemical synthesis of biomolecules. In addition, spectrometric and spectroscopic techniques, such as UV-visible, infrared, mass spectroscopy, nuclear magnetic resonance, and coupled techniques for the chemical characterization and identification of active substances. For some of the identified compounds were performed studies of molecular docking *in silico*.

Table 1 lists some of the medicinal plants studied in the LFUAMI. Among the most relevant are *Tillandsia* spp (“heno”), *Hibiscus sabdariffa* (“Jamaica”), *Psacalium* spp (“matarique”), *Cecropia obtusifolia* (“guarumbo”), *Catharanthus roseous* (“vinca”), *Ibervillea sonorae* (“wereque”), *Smilax dominguensis* (“cocolmeca”), *Punica granatum* (“granada”), *Tagetes lucida* (“pericón”) and *Cucurbita ficifolia* (“chilacayote”) among other. In addition to medicinal plants, our research has extended to include the study of marine seagrasses, the beetle *Ulomoides dermestoides*, and jellyfish. Through collaborative efforts with various laboratories from other national institutions, we have successfully identified and isolated several active compounds from these natural resources. Some of these compounds are detailed in Table 2: triterpenes, such as α-amyrin, lupeol, oleanolic acid, and ursolic acid; phenolic acids, chlorogenic acid, and 4-hydroxybenzoic acid; flavonoids, such as luteolin, kaempferol, quercetin, apigenin and rutin; D-*chiro*-inositol, and a variety of compounds of lipidic nature, such as β-sitosterol, lauric acid, oleic acid, among others. Other supplements or drugs with interesting properties were also studied, such as glycine, cannabidiol, metformin, and rosiglitazone, among other compounds of natural or synthetic origin (Table 2). These compounds originate from diverse natural and synthetic sources and hold promise for further pharmacological investigation and potential therapeutic applications. These plants and compounds were evaluated in our laboratory throughout different experimental conditions, showing diverse activities with utility in metabolic diseases, such as anti-diabetic, hypoglycemic, anti-inflammatory, antioxidant, hypolipidemic, vasorelaxant, antihypertensive, and, particularly in the treatment of the MS. In addition to UAM-Iztapalapa, several other institutions have been involved in

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these investigations, including UAM- Xochimilco, Chemical Institute (UNAM), FES Iztacala (UNAM), Facultad de Farmacia (UAEM), Specialties Hospital (IMSS), Centro de Investigación Biomedica del Sur (CIBIS-IMSS), Escuela Superior de Medicina (IPN), Instituto Nacional de Nutrición "Salvador Zubiran," Instituto Nacional de Cardiología "Ignacio Chávez," Hospital de Pediatría, Hospital Infantil de México "Federico Gómez," to mention a few. We sincerely thank all researchers from other institutions who have supported us. These collaborations have been instrumental in advancing our research and development objectives related to the study of natural and synthetic products.

Among the myriad resources investigated within our laboratory, particular attention must be drawn to the exhaustive research conducted on the fruit of *Cucurbita ficifolia* (*C. ficifolia*), colloquially known as chilacayote. This fruit, with its rich history of empirical use in our country for managing diabetes, has been the focal point of our research endeavors. Through rigorous chemical and pharmacological investigations at the experimental level, our research group has uncovered significant insights into the therapeutic potential of *C. ficifolia*. The elucidation of its bioactive components and pharmacological properties represents a milestone achievement, showcasing the transformative impact of our research efforts. Moreover, our findings hold promise for advancing our understanding of traditional remedies and potentially developing novel treatments for metabolic disorders. Thus, the research surrounding *C. ficifolia* stands as a testament to the dedication and innovation of our research group in the pursuit of scientific knowledge and its application to improve human health. In studying this engaging edible and medicinal resource, its investigation resulted in some technological developments in vias of scalation and marketing. In the next section, two special contributions of the LFUAMI, the technological development of nutraceutical products from *C. ficifolia* fruit and the in-silico analysis using a simplified method to perform molecular coupling simulations assisted by a computer, will be discussed.

Technological period (2021-)

The culmination of these extensive studies, which began with *in vivo* and *in vitro* experimentation and progressed to the application of *in silico* simulation methods, represents a significant milestone in the history of the LFUAMI. This milestone is embodied by the fruit of *C. ficifolia*, an engaging edible and medicinal resource of Mexican medicinal, whose study was initially proposed by Dr. Rubén Roman [12]. It represents some of the transcendent results in chemical and pharmacological research by our research group, culminating in a technological development with potential to commercialization. Another milestone in the history of the LFUAMI is its contribution to computer-assisted rational drug design. Both situations will be commented in the next section.

Chemical and Pharmacological Studies of the fruit of *C. ficifolia* and its technological development

Extracts were derived from the juice of mature fruits and subjected to chemical characterization. The aqueous extract demonstrated antihyperglycemic effects in both healthy rabbits and those with alloxan-induced diabetes, as well as in healthy rats and mice and those with streptozotocin-induced diabetes, in both acute and subacute studies [11-12], [26-27]. Normal mice had No toxic effects at usual doses [28]. In addition, the extract increased insulin levels in healthy animals and RINm5F cells, increasing the calcium store and insulin RNAm expresion, which was corroborated by confocal microscopy and RT-qPCR, respectively [33-34]. Regarding its extra-pancreatic effects, quantitative and histological assessments using Periodic Acid-Schiff (PAS) staining revealed an increase in liver glycogen accumulation. This regulation of glycogen synthesis enzymes and phosphorylase activity was validated through Western Blot analysis [36]. In mice with streptozotocin-induced diabetes, it was demonstrated that the expression of PPAR-α in the liver is increased, a transcription factor involved in lipid metabolism, without affection on PPAR-γ [39]. The antioxidant effect was evaluated in different organs due to *C. ficifolia* in this same model. Increased GSH and decreased malondialdehyde were observed in the liver, kidney, and heart [29]. The antioxidant effect was also observed in mice with STZ-induced diabetes and 3T3-L1 adipocytes, with increased GSSG/GSH ratio, glutathione peroxidase, and reductase glutathione, with a decrease in hydrogen peroxide. These findings confirm the antioxidant action of *C. ficifolia* [30,32]. The anti-inflammatory action of *C. ficifolia* was investigated in mice with monosodium glutamate-

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induced obesity. After 30 days of extract administration, two pro-inflammatory cytokines, TNF-α and resistin, were reduced [35]. Similar findings were observed in vitro using 3T3-L1 adipocytes, where protein and expression levels of TNF-α and IL-6 were measured [32]. In summary, C. *ficifolia* exhibited hypoglycemic, antioxidant, and anti-inflammatory effects, as demonstrated in different experimental models, including studies involving type 2 diabetic patients [98-99].

Concerning the chemical components of the fruit, previous studies have suggested D-*chiro* inositol (DCI), an isomer mediating insulin action, as one of the main constituents that may be participating in the above actions [101-102]. DCI is also an activator of the glycogen synthase and pyruvate dehydrogenase enzymes, regulates the oxidative stress in adipocytes, exhibits reduction of pro-inflammatory cytokines (TNF-α, IL-6, and resistin), preventing the inflammatory damage in adipocytes 3T3-L1. In these studies, performed in our laboratory, DCI also increased the PKB activation, exhibiting insulin-mimetic effects in 3T3-L1 adipocytes [32]. Therefore, this compound may be beneficial for treating obesity and non-insulin-dependent diabetes mellitus (103) and should be considered in future studies.

The fruit also contains phenolic acids such as *p*-coumaric acid, *p*-hydroxybenzoic acid, *p*-hydroxyphenyl acetic acid, and gallic acid; the flavonoid catechin; salicin, and phytosterols such as stigmast-7,22-dien-3-ol and stigmast-7-en-3-ol, β-sitosterol, among others [36,95]. It has been suggested that all these compounds may act in synergy, explaining their multiple pharmacological effects and their health benefits, sometimes equivalent to agents used to control type 2 diabetes [36].

It is clear then that the data that are so far available in research into the medicinal properties and chemical components of the fruit of *C. ficifolia* sustain insulin-secretagogue action, as well as hypolipemic, anti-inflammatory, and antioxidant properties. The evidence suggests that this fruit may help treat metabolic diseases; however, for massive use, it is necessary to examine other aspects, such as its acceptability, applicability, feasibility, and transfer in different contexts. In addition, it is essential to explore pharmacokinetic processes associated with active molecules and metabolites.

Therefore, we propose using this fruit as a raw material for developing bio-functional foods, nutraceutical ingredients, and phyto-medicines that can be useful in controlling MS and associated diseases. Promoting the utilization of this fruit in the processing of bio-functional foods could have a dual impact. Not only could it directly enhance the population's health, but it also presents economic opportunities by stimulating cultivation and increasing production of this plant, bolstering the economies of the regions where it is grown. It also provides viable alternatives for producing healthy food and ingredients that meet the dietary needs of the population.

In this regard, thanks to the support of Dr. Socorro Josefina Villanueva-Rodríguez, researcher at the Food Technology and Assistance Center of the State of Jalisco, AC (CIATEJ), who held a sabbatical stay at the UAM-I Pharmacology Laboratory, four product proposals were obtained based on the fruit of *C. ficifolia*. After characterizing the bromatological and phytochemically properties of the raw material (chilacayote fruit), several formulations of nutraceutical juices, instant soups, nutritional boots, and a phyto-medicine were obtained and studied. These formulations underwent a sensory evaluation to select the most acceptable products for potential commercialization. The selected formulations were again subjected to physicochemical, phytochemical, bromatological, and biological assessments. Their components (polyphenols, phytosterols, flavonoids, sugars, and carotenoids), antioxidant capacity (DPPH and ABTS), and glycemic effects were determined with encouraging results.

We must stress that the food and nutraceutical utility of these preparations is based on the results obtained from the basic research carried out with the fruit of *C. ficifolia* in what goes this century by our working group of LFUAMI. Today, there is a need to continue the expansion of these technological advances, which help treat metabolic diseases and reach their massive use.

Pharmacology laboratory and its contribution to the rational design of computer-assisted drugs

Molecular docking has become a powerful computational tool for new drug research and design, playing a pivotal role in predicting interactions between drug-related ligands and their potential receptors [104]. Table 3 lists some of the analyzed compounds in LFUAMI, in collaboration with other institutions, by molecular docking. Since our in vivo and in vitro research is about metabolic activities, the receptors involved are related to modulating actions of carbohydrate and lipid metabolism, such as PPAR-α, PPAR-γ, PPAR-δ, GPR40, and

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α-glucosidase enzyme, among others. The compounds investigated have generally resulted in multitarget activity, which might represent certain therapeutic advantages for treating complex diseases such as MS.

Although these results reinforce the potential utility of the compounds studied, more extensive studies of simulation in silico involving other types of metabolism regulatory receptors are still needed. However, molecular docking and the virtual screening simulation software currently available require researchers to make numerous configurations and navigate unintuitive menus, which requires significantly optimizing the process. Therefore, there is a pressing need to design a cohesive set of computational programs to expedite work with multiple ligands and receptors while simplifying simultaneous simulations. Such a framework would greatly facilitate the adoption of these techniques by researchers seeking to explore new ligands.

In this context, our laboratory has designed an accessible and user-friendly open-source software, which provides a robust format for presenting results and with a format simple for interpreting large amounts of data. This tool is extensively described in another article of this volume of the *Journal of Mexican Chemical Society*. The idea was to develop a simple yet reliable tool to manage the molecular docking process. Furthermore, the program's source code is free and has perpetual access to local computational resources.

When facing virtual screenings with extensive libraries of ligands and target proteins, this tool saves valuable research time and investment of monetary resources from the budget in subscription plans for online services. The tool was built using existing molecular docking software. From there, a suite of interconnected computer programs has been meticulously designed with dual objectives: to accelerate workflows involving numerous ligands and target proteins and to streamline simulations, thus making these techniques more accessible. Thus, the tool was conceived as open-source software, free and simple to use. Furthermore, one of the objectives was to create a robust results presentation format conceptualized as a massive report of rows and columns. In this way, the large amount of data obtained is intended to be easy to filter, discriminate, and interpret. This automated computational tool capable of performing multiple simultaneous molecular docking studies offers a significant advantage in this field, because it automates the preparation of ligands and receptors for the docking simulation, generates configuration files for each docking process, executes docking and site preparation procedures concurrently, and organizes comprehensive reports detailing the simulation results. The idea is that this proposal will greatly facilitate the widespread adoption of this instrument to explore new therapeutic targets. The proposal of this instrument is already widely disseminated through standard communication channels within the scientific community. Information for accessing the program is now available in another article in this volume of the *Journal of Mexican Chemical Society*.

Present and future

The LFUAMI has significantly contributed to the discovery and development of medicines. Many of the resources investigated have the potential to be utilized as raw materials for the development of functional foods, phyto-medicines, and pharmaceuticals. However, clinical assessments and their implementation in the therapeutic still need to be initiated. LFUAMI now has everything necessary to continue to carry out high-quality research in the field of pharmacology, applying cutting-edge research techniques associated with the evaluation of medicines with a potential use for the treatment of metabolic diseases, including diabetes mellitus, obesity, dyslipidemias, hypertension, inflammation and oxidant stress, among others, with the ability to support research from other research groups in our university and other institutions at request, promoting collaboration and facilitating wider research initiatives.

It is essential to emphasize that the research achievements of the LFUAMI have been made possible through collaborative agreements with various institutions both within the country and abroad, including inter-institutional partnerships and collaborations within our university. Additionally, we owe much gratitude to the dedicated students who have contributed to our laboratory, choosing to pursue their research projects with us. Their tireless efforts have been crucial to moving forward in our research goals and we sincerely appreciate his commitment and contributions. LFUAMI has received more than 300 students for research activities. Our efforts have led to the publication of more than 120 articles, which have over 5000 citations. These significant outputs underscore the LFUAMI's commitment to fostering student involvement and its dedication to producing

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impactful research outcomes in pharmacological research, contributing in a relevant manner to the state of the art in this area of knowledge.

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Table 1. Medicinal resources studied at LFUAMI in collaboration with other laboratories from national and international institutions.

Scientific name	Family	Used part	Preparation	Experimental model	References
1. *Acourtia thurberi* (A. Gray) Reveal & R.M. King.	Asteraceae	Rhizome	Decoction	Fasted normal mice GTT in rabbits	[10]
2. Agastache mexicana (Kunth) Lint &Epling)	Lamiaceae	Complete	Organic extract	GTT in mice Phytochemical analysis	[105]
3. *Allium cepa* L.	Amaryllidaceae	Bulb	Decoction	GTT in rabbits	[11]
4. *Allium sativum* L.	Amaryllidaceae	Bulb	Decoction	GTT in rabbits	[11]
5. *Aloe barbadensis* Mill.	Asphodelaceae	Stems	Juice Polyphenolic extract from the gel	GTT in rabbits. Mice with insulin-resistance	[12] [13]
6. Aquillea millefolium L.		Flowers	Organic extract	GTT in mice Phytochemical analysis	[106]
7. *Artemisia mexicana* Willd. ex Spreng.	Asteraceae	Complete	Decoction	GTT in rabbits	[14]
8. *Astianthus viminalis* (Kunth) Baill.	Bignoniaceae	Leaves	Decoction	GTT in rabbits	[14]
9. *Banisteriopsis caapi* (Spruce ex Griseb.) C.V. Morton and *Psychotria viridis* Ruiz & Pav. (ayahuasca)	Malpighiaceae Rubiaceae	Leaves and stem	Decoction	Review and a toxicologic clinical case	[15-16]
10. Bauhinia divaricata L.	Fabaceae	Leaves	Decoction	GTT in rabbits	[17]
11. *Bidens odorata* Cav.	Asteraceae	Leaves and branches	Organic extracts Fat acids	Castor oil-induced diarrhea mice Carbachol-induced ileum contraction in rats	[18]
12. *Bidens pilosa* L.	Asteraceae	Complete	Decoction	GTT in rabbits	[14]
13. Bocconia arborea S. Watson	Papaveraceae	Complete	Organic extract	GTT in mice and Phytochemical analysis	[107]
14. *Brassica oleracea* L.	Brassicaceae	Inflorescence	Juice	GTT in rabbits	[11]
15. Brassica oleracea L. var. *botrytis*	Brassicaceae	Leaves	Juice	GTT in rabbits	[11]
16. *Buddleia americana* L.	Scrophulariaceae	Flowers	Decoction	GTT in rabbits	[17]

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Scientific name	Family	Used part	Preparation	Experimental model	References
17. *Calea zacatechichi* Schltdl.	Asteraceae	Inflorescence	Decoction	GTT in rabbits	[17]
18. *Cannabis* L. sp	Cannabaceae	Inflorescence	Comercial oil	Review 3T3-L1 adipocytes	[7] [Outcome unpublished]
19. *Catharanthus roseous* (L.) G. Don	Apocynaceae	Flower, leaves, stem, and roots.	Aqueous and organic extracts. Phenolic- fraction	Normal mice. 3T3- L1 adipocytes Alloxan-induced diabetic mice. RINm5F pancreatic cells	[19,20,21]
20. *Caulerpa sertularioides* (S.G. Gmelin) M. Howe (Chlorophyta)	Caulerpaceae	Complete	Aqueous extract	STZ-induced diabetes mice	[22]
21. *Cecropia obtusifolia* Bertol.	Urticaceae	Leaves	Decoction Aqueous extract	GTT in rabbits RINm5F pancreatic cells	[12,23]
22. *Cleoserrata serrata* (Jacq.) Iltis	Cleomaceae	Aerial parts	Organic extracts. Polyphenol mixture	TPA- and carrageenan-induced inflammation	[24]
23. *Citrus aurantium* L.	Rutaceae	Fruit	Juice	GTT in rabbits	[14]
24. *Cnidoscolus multilobus* (Pax) I.M. Johnst.	Euphorbiaceae	Leaves	Decoction	GTT in rabbits	[14]
25. *Coix lachryma-jobi* L.	Poaceae	Seems	Decoction	GTT in rabbits	[17]
26. *Crataegus pubescens* (C. Presl) C. Presl	Rosaceae	Root	Decoction	GTT in rabbits	[17]
27. *Cucumis sativus* L.	Cucurbitaceae	Fruit	Juice Fractions from aqueous extract (containing glycine, asparagine, and arginine)	GTT in rabbits Dysfunctional 3T3-L1 adipocytes	[11,25]
28. *Cucurbita ficifolia* Bouché	Cucurbitaceae	Fruit	Juice Aqueous extract Fraction from aqueous extract (containing chlorogenic acid) Fermented juice	GTT in rabbits Normal mice Alloxan-induced diabetic rabbits and mice STZ-induced diabetes mice MSG-induced obese mice	[11-12, 26-39]

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				Rat aortic rings 3T3-L1 adipocytes RINm5F pancreatic cells HepG2 Hepatocytes	
Scientific name	**Family**	**Used part**	**Preparation**	**Experimental model**	**References**
29. *Cuminum cyminum* L.	Apiaceae	Seeds	Decoction	GTT in rabbits	[11]
30. *Cynodon dactylon* (L.) Pers.	Poaceae	Complete	Decoction	GTT in rabbits	[17]
31. *Eriobotrya japonica* (Thunb.) Lindl.	Rosaceae	Leaves	Decoction	GTT in rabbits	[12]
32. *Eucaliptus globulus* Labill.	Myrtaceae	Leaves	Decoction	GTT in rabbits	[12]
33. *Euphorbia preslii* Guss.	Euphorbiaceae	Complete	Decoction	GTT in rabbits	[14]
34. *Euphorbia prostrata* Aiton	Euphorbiaceae	Complete	Decoction	GTT in rabbits	[14]
35. *Exostema caribeaum* (Jacq.) Roem. & Schult.	Rubiaceae	Bark	Decoction	GTT in rabbits	[14]
36. *Eysenhardtia polystachya* (Ortega) Sarg.	Fabaceae	Stem	Decoction	GTT in rabbits	[14]
37. *Mangostana cambogia* Gaertn. *(Syn.: Garcinia cambogia* (Gaertn.) Desr.	Clusiaceae	N.I.	Formulation	Obese patients	[4]
38. *Guaiacum coulteri* A. Gray.	Zygophylaceae	Bark	Decoction	GTT in rabbits Alloxan-induced diabetic rabbits	[12,26]
39. *Guazuma ulmifolia* Lam.	Malvaceae	Leaves	Decoction	GTT in rabbits	[14]
40. *Hibiscus sabdariffa* L.	Malvaceae	Calyces	Aqueous extract. Dichloromethane extract Triterpenoids	MSG-induced obese mice Diuresis in rats Diuresis in in situ kidney model GTT in mice 3T3-L1 adipocytes	[40-42]

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Scientific name	Family	Used part	Preparation	Experimental model	References
41. *Ibervillea sonorae* (S. Watson) Greene	Cucurbitaceae	Root	Monoglycerides Fat acids	Normal and diabetic mice and rats. Rat aortic rings 3T3-L1 adipocytes	[19,43-46]
42. *Jatropha dioica* Sessé ex. Cerv.	Euphorbiaceae	Roots	Decoction	GTT in rabbits	[14]
43. *Jatropha neopauciflora* Pax.	Euphorbiaceae	Latex	Phenols and flavonoids	Antimicrobial and antifungal models Wound healing tensiometric method. Normal and diabetic mice.	[47-48]
44. *Lactuca sativa* L.	Asteraceae	Leaf	Juice	GTT in rabbits	[11]
45. *Lepechinia caulescens* (Ortega) Epling	Lamiaceae	Leaf and stem	Decoction	GTT in rabbits Alloxan-induced diabetic rabbits. Normal mice 3T3-L1 adipocytes	[12,14, 19,26]
46. *Mangifera indica* L.	Anacardiaceae	Leaves	Decoction	GTT in rabbits	[14]
47. *Marrubium vulgare* L.	Lamiaceae	Complete	Decoction	GTT in rabbits	[17]
48. *Mentha piperita* L.	Lamiaceae	Complete	Decoction	GTT in rabbits	[14]
49. *Musa ensete J.F. Gmel.*	Musaceae	Seems	Decoction	Normal mice 3T3- L1 adipocytes	[19]
50. *Musa sapientum* L.	Musaceae	Flowers	Decoction	GTT in rabbits	[14]
51. *Olea europaea* L.	Oleaceae	Leaves	Decoction	GTT in rabbits	[14]
52. *Opuntia ficus indica* (L.) Mill.	Cactaceae	Stem	Juice Polysaccharides	GTT in rabbits Normal mice GTT in mice Alloxan-induced diabetes mice	[14,49]
53. *Opuntia streptacantha* Lem.	Cactaceae	Stem	Juice Polysaccharides	Pancreatectomized rabbits A clinical case GTT in rabbits Normal mice GTT in mice Alloxan-induced diabetes mice	[1-3,11-12,49]

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Scientific name	Family	Used part	Preparation	Experimental model	References
54. *Parmentiera edulis* Raf.	Bignoniaceae	Fruit	Juice	GTT in rabbits	[14]
55. *Pavonia schiedeana* Steud.	Malvaceae	Leaf	Decoction	GTT in rabbits	[17]
56. *Persea americana* Mill.	Lauraceae	Seems	Decoction	GTT in rabbits	[14]
57. *Phaseolus vulgaris* L.	Fabaceae	Pod	Decoction	GTT in rabbits	[11-12]
58. *Physalis philadelphica* Lam.	Solanaceae	Calices of the fruit	Decoction	GTT in rabbits	[17]
59. *Plantago major* L.	Plantaginaceae	Seeds	Aqueous and organic extracts	Normal Alloxan-induced diabetes mice Normal mouse cells Transformed human cells	[50-51]
60. *Psacalium decompositum* (A. Gray) H. Rob. & Brettell	Asteraceae	Rhizome	Decoction Aqueous and organic extracts Sesquiterpenoids Polysaccharide fractions Fructooligosaccharides	GTT in rabbits. Fasted normal mice Alloxan-induced diabetes mice Normal rats Fructose-induced obese rats	[10,52-56]
61. *Psacalium peltatum* (Kunth) Cass.	Asteraceae	Rhizome	Decoction	GTT in rabbits Alloxan-induced diabetes rabbits Fasted normal mice Alloxan-induced diabetes mice STZ-induced diabetes-mice	[10,12,26, 57-59]
62. *Psidium guajava* L.	Myrtaceae	Fruit	Juice	GTT in rabbits	[11]
63. *Punica granatum* L.	Lythraceae	Peels	Aqueous extract	Normal mice GTT in mice STZ-induced diabetes mice Antioxidant capacity *in vitro*	[60]
64. *Randia echinocarpa* DC.	Rubiaceae	Fruit	Decoction	GTT in rabbits	[14]
65. *Rauvolfia tetraphylla* L.	Apocynaceae	Leaves	Decoction	GTT in rabbits	[14]

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Scientific name	Family	Used part	Preparation	Experimental model	References
66. *Rhizophora mangle* L.	Rhizophoraceae	Stem	Decoction	GTT in rabbits	[14]
67. *Salpianthus macrodonthus* Standl.	Nyctaginaceae	Leaf and stem. Roots	Decoction	GTT in rabbits	[12,14]
68. *Salvia polystachya* M. Martens & Galeotti	Lamiaceae	Complete	Terpenoids	GTT in mice	[61]
69. *Senna crotalaroides* (Kunth) H.S. Irwin & Barneby	Fabaceae	Leaf and stem. Roots	Chloroform extract	TPA-induced ear edema, cytotoxic activity	[62]
70. *Senna skinneri* (Benth.) H.S. Irwin & Barneby	Fabaceae	Leaves	Decoction	GTT in rabbits	[15]
71. *Senna villosa* (Mill.) H.S. Irwin & Barneby	Fabaceae	Leaf and stem. Roots	Chloroform extract	TPA-induced ear edema	[63]
72. *Serjania triquetra* Radlk.	Sapindaceae	Stem	Decoction	GTT in rabbits	[14]
73. *Solanum verbascifolium* L.	Solanaceae	Leaves and stem	Decoction	GTT in rabbits	[12]
74. Smilax dominguensis Willd.	Smilacaceae	Root	Chloroform extract	GTT in mice Phytochemical analysis	[Outcome unpublished]
75. *Spinacia oleracea* L.	Amaranthaceae	Leaves	Juice	GTT in rabbits	[11]
76. *Spyridia filamentosa* (Wulfen) Harvey (Rhodophyta)	Spyridiaceae	Complete	Aqueous extract	STZ-induced diabetes mice	[64]
77. *Tagetes lucida* Cav.	Asteraceae	Aerial parts	Aqueous extract	Antidepressive forced swimming test	[65-67]
78. *Bignonia stans L. (Syn.: Tecoma stans* (L.) Juss. ex Kunth	Bignoniaceae	Leaf and stem	Decoction	GTT in rabbits	[12]
79. *Teucrium cubense* Jacq.	Lamiaceae	Leaf and stem	Decoction	GTT in rabbits	[12]
80. *Thalassia testudinum* Banks & Sol. ex K.D. Köning (marine phanerogam)	Hydrocharitaceae	Complete	Aqueous extract	Hemolytic activity Phytochemical analysis	[68]
81. *Tillandsia recurvata* (L.) L.	Bromeliaceae	Complete	Aqueous extract	Normal and diabetic mice	[69]

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Scientific name	Family	Used part	Preparation	Experimental model	References
82. *Tillandsia usneoides* (L.) L.	Bromeliaceae	Complete	Flavone	Review C2C12 myoblasts Hepatocytes RINm5F pancreatic cells	[70-72]
83. *Vaccinium angustifolium* Aiton	Ericaceae	Fruit	Fermented juice with *Serratia vaccinii* bacteria Anthocyanins and proanthocyanidins	3T3-L1 adipocytes	[73]
84. *Heliotropium verdcourtii Craven (Syn.: Tournefortia hirsutissima* L.	Heliotropiaceae	Stem	Decoction	GTT in rabbits	[14]
85. *Trigonella foenum-graceum* L.	Fabaceae	Seeds	Decoction	GTT in rabbits	[14]
86. *Turnera diffusa* Willd.	Passifloraceae	Leaves	Decoction	GTT in rabbits	[14]
87. *Ulomoides dermestoides* Chev. (beetle)		Complete	Lipid fraction	STZ-induced diabetes mice	[74]
88. *Urtica dioica* L.	Urticaceae	Complete	Decoction	GTT in rabbits	[17]

GTT=Glucose tolerance test; STZ=Streptozotocin; MSG=monosodium glutamate.

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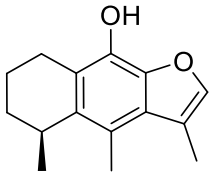
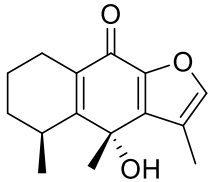
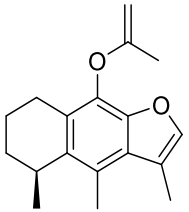
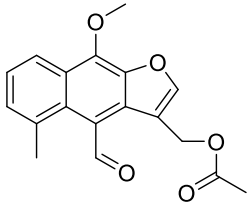
Table 2. Compounds identified and studied in LFUAMI in collaboration with other laboratories from national and international institutions.

Compound name	Chemical Structure	Origin	Biological activity	References
1. Cacalol		*Psacalium decompositum*	Anti-inflammatory	[53,5]
2. Cacalone		*Psacalium decompositum*	Anti-inflammatory	[53,75]
3. Cacalol acetate		*Psacalium decompositum*	Anti-inflammatory	[76]
4. Maturin acetate		*Psacalium decompositum*	Immuno-stimulator	[53,77]

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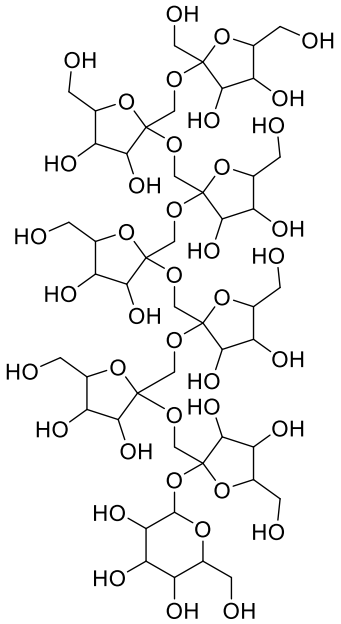
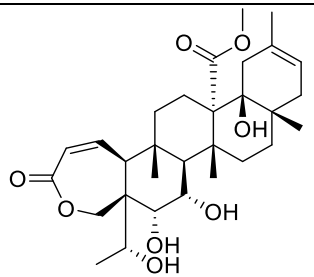
Compound name	**Chemical Structure**	**Origin**	**Biological activity**	**References**
5. Fructo-oligosaccharides		*Psacalium decompositum*	Hypoglycemic. Anti-inflammatory.	[54-55]
6. Galphimine-A		*Galphimia glauca*	Anxiolytic	[78]

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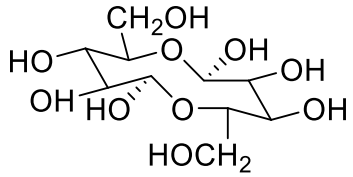
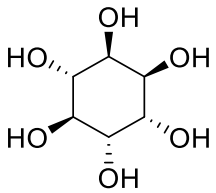
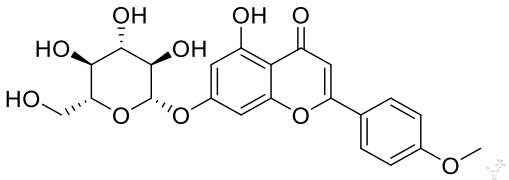
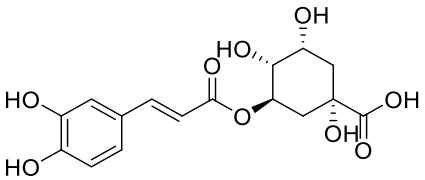
Compound name	Chemical Structure	Origin	Biological activity	References
7. Peltalose		*Psacalium peltatum*	Hypoglycemic	[59,100]
8. D-*chiro*-inositol		*Cucurbita ficifolia*	Anti-inflammatory. Hypoglycemic. Antioxidant.	[32]
9. Tilianin		*Agastache mexicana*	Anti-diabetic. Anti-hyperlipidemic. Anti-inflammatory.	[79]
10. Chlorogenic acid		*Cecropia obtusifolia*	Dual agonist: Insulin-secretagogue and PPAR agonist	[9]

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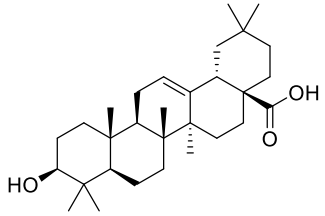
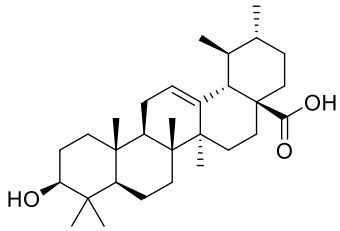
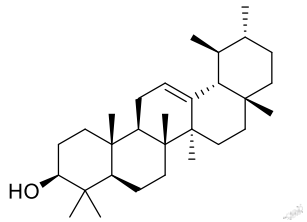
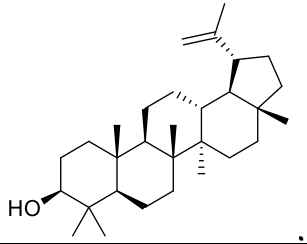
Compound name	**Chemical Structure**	**Origin**	**Biological activity**	**References**
11. Oleanolic acid		*Salvia polystachia*	PPAR dual agonist. Hypo-glycemic. Antihyperglycemic. α-glucosidases inhibitor.	[61,80]
12. Ursolic acid		*Salvia polystachia*	Hypoglycemic. Antihyperglycemic. α-glucosidases inhibitor.	[61]
13. α-amyrin		*Hibiscus sabdariffa*	Antihyergly-cemic. PPAR-dual agonist AMPK-allosteric activator Insulino-mimetic	[42,81]
14. Lupeol		*Hibiscus sabdariffa*	Antihyperglycemic PPAR-dual agonist.	[42]

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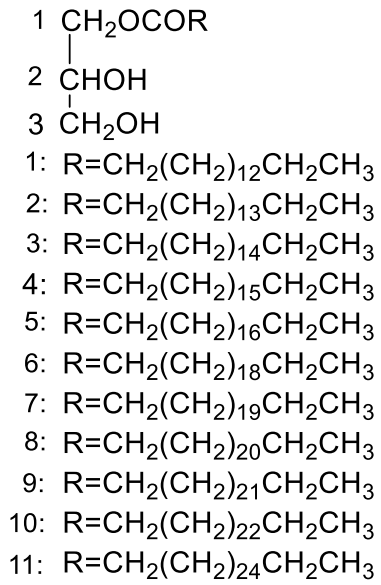
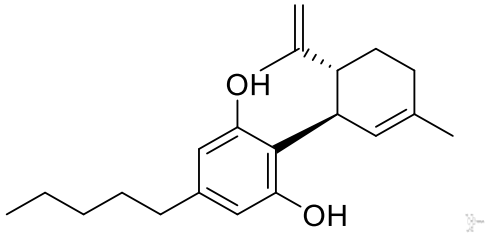
Compound name	Chemical Structure	Origin	Biological activity	References
15. Monoglyceride mixture		*Ibervillea sonorae*	Hypoglycemic	[45]
16. Cannabidiol		*Cannabis* sp.	Ani-inflammatory	[Outcome unpublished]

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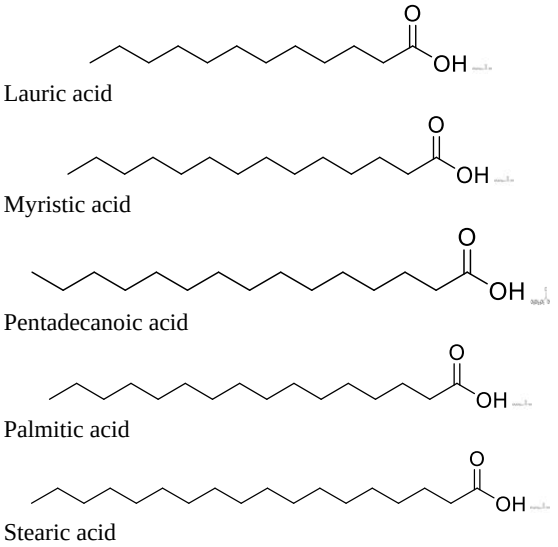
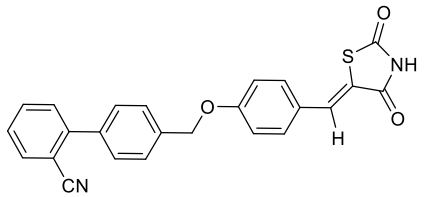
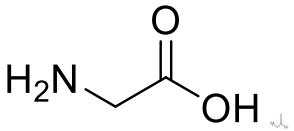
Compound name	Chemical Structure	Origin	Biological activity	References
17. Fat acids mixture		*Ibervillea sonorae*	Hypoglycemic	[45]
18. 4′-({4-[(Z)-(2,4-dioxo-1,3-thiazolidine-5-ylidene)-ethyl]-phenoxy}methyl)-1,1′-biphenyl-2-carbonitrile		Synthetic	Anti-diabetic. PPAR-dual agonist.	[82]
19. Glycine		Aminoacid	Anti-inflammatory. Antioxidant Inhibitor. competitive of the TNF-α receptor	[83-89]

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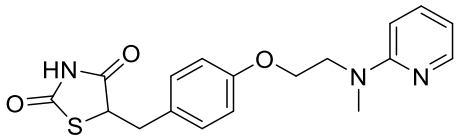
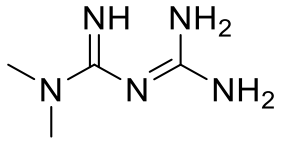
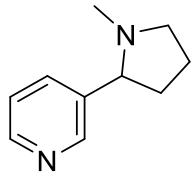
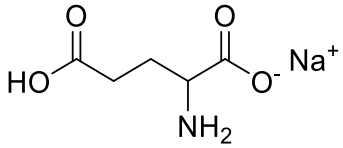
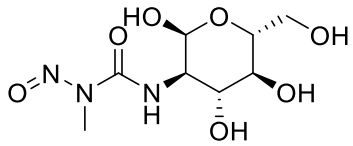
Compound name	Chemical Structure	Origin	Biological activity	References
20. Rosiglitazone		Synthetic	Insulin-sensitizer	[5-6]
21. Metformin		Synthetic	Insulin-sensitizer	[6]
22. Nicotine		Synthetic	Anti-depressant	[90]
23. Monosodium glutamate		Synthetic	Toxicity metabolic Inducer of obesity	[91-92]
24. Streptozotocin		*Streptomyces achromogenes*	Inducer of experimental diabetes	[93]

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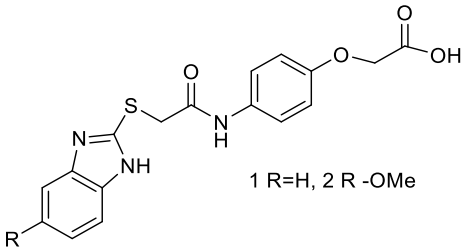
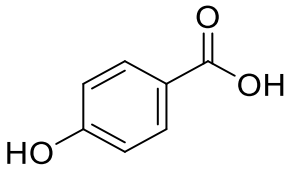
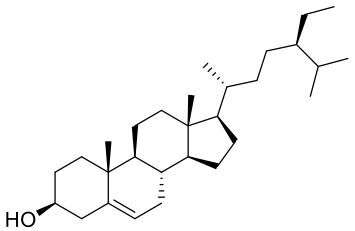
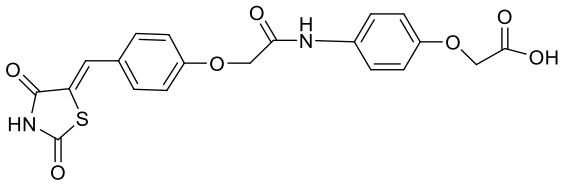
Compound name	Chemical Structure	Origin	Biological activity	References
25. 2-(4-(2-((1H-benzo[d]imidazol-2-yl)thio)-acetamido)phenoxy) acetic acid (**1**), and 2-(4-(2-((5-methoxy-1H-benzo[d]imidazol-2-yl)thio)-acetamido)-phenoxy)-acetic acid (**2**)		Synthetics	Anti-diabetic. PPARγ/ GPR40 dual agonists	[94]
26. 4-hydroxybenzoic acid		*Cucurbita ficifolia*	Insulin-secretagogue PPAR agonist Liver glycogen storage promotor	[95]
27. β-sitosterol		*Cucurbita ficifolia*	Insulin-secretagogue PPAR agonist Liver glycogen storage promotor	[95]
28. {4-[({4-[(Z)-(2,4-dioxo-1,3-thiazolidine-5-ylidene)-methyl]-phenoxy} acetyl)amino]-phenoxyacetic acid		Synthetic	Anti-diabetic in non-insulin-dependent diabetes rats	[96]

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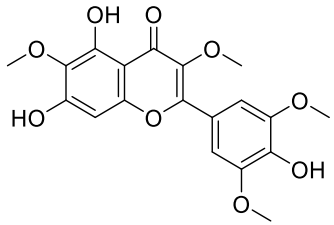
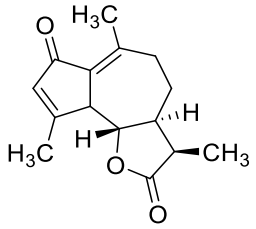
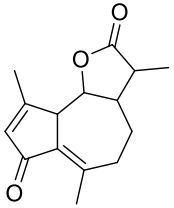
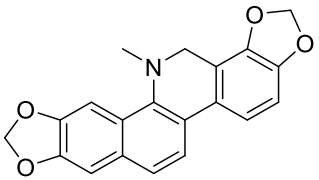
Compound name	Chemical Structure	Origin	Biological activity	References
29. 5,7,4´-trihydroxy-3,6,3',5´-tetramethoxyflavone		*Tillandsia usneoides*	Antihyperglycemic	[97]
30. Achillin		*Achillea millefolium*	Antidiabetic	[105]
31. Leucodin		*Achillea millefolium*	Antidiabetic	[105]
32. Dihydrosanguinarine		*Bocconia aerboria*	Anti-nociceptive	[106]

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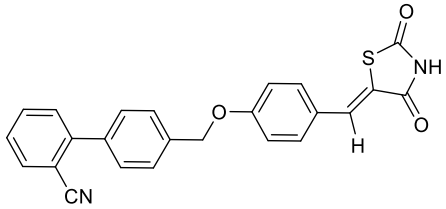
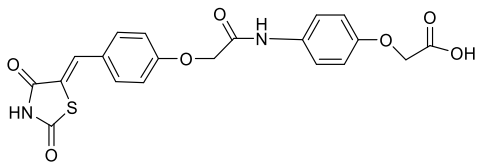
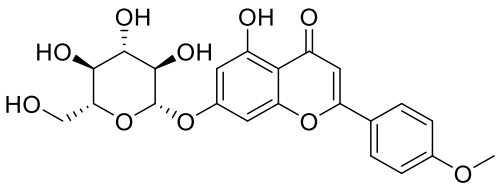
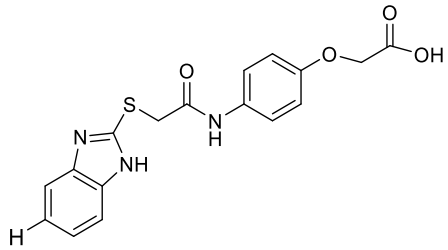
Table 3. Some analyzed compounds in UAM´s pharmacology laboratory with collaboration with other institutions by molecular docking and their potential biological activity.

Compounds	Chemical structure	Receptors	Potencial activity	Referencias
4′-({4-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene) methyl]-phenoxy} methyl)-1,1′-biphenyl-2-carbonitrile		PPAR-α PPAR-γ	PPAR-α/γ dual agonist	[82]
{4-[({4-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)-methyl]-phenoxy} acetyl)-amino] phenoxy} acetic acid		PPAR-γ	PPAR-γ agonist	[96]
Tilianin		PPAR-α	PPAR-α agonist	[79]
2-(4-(2-((1H-benzo[d]imidazol-2-yl)thio)acetamido)-phenoxy)-acetic acid		PPAR-γ GPR40	PPAR-γ/GPR40 dual agonist	[94]

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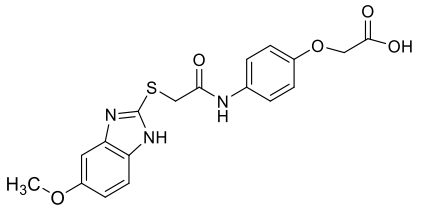
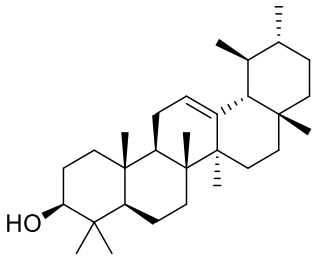
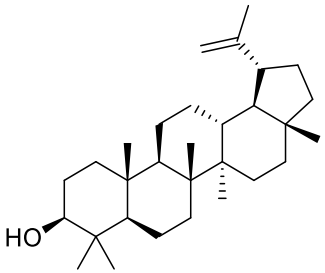
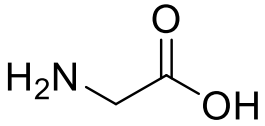
Compounds	**Chemical structure**	**Receptors**	**Potencial activity**	**Referencias**
2-(4-(2-((5-methoxy-1H-benzo[d]imidazol-2-yl) thiol)-acetamido)-phenoxy)-acetic acid		PPAR-γ GPR40	PPAR-γ/GPR40 dual agonist	[94]
α-amyrin		PPAR-δ PPAR-γ AMPK	PPAR-δ/-γ dual agonist AMPK allosteric activator	[42,81]
Lupeol		PPAR-δ PPAR-γ	PPAR-δ/-γ dual agonist	[42]
Glycine		TNF-α1	TNF-α partial agonist	[89]

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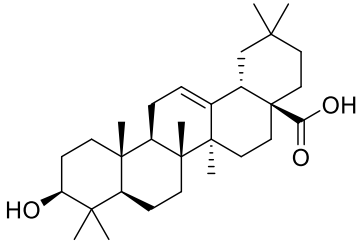
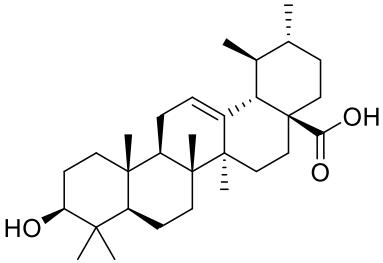
Compounds	**Chemical structure**	**Receptors**	**Potencial activity**	**Referencias**
Oleanolic acid		α-glucosidase SGLT1	α - glucosidase inhibitor SGLT1 inhibitor	[61]
Ursolic acid		α-glucosidase SGLT1	α - glucosidase inhibitor SGLT1 inhibitor	[61]