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Revisión / Review

On the first book of medicinal plants written in the American Continent: The *Libellus Medicinalibus Indorum Herbis* from Mexico, 1552. A review

[Sobre el primer libro de plantas medicinales escrito en el Continente Americano: El *Libellus Medicinalibus Indorum Herbis* de México, 1552. Una revisión]

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Abstract: The "*Libellus de Medicinalibus Indorum Herbis*" (Little Book of Indian Medicinal Plants) was composed by the indigenous sages Martín De la Cruz and Juan Badiano, 31 years after the Aztec Empire fall. The former was the author, and the latter translated the manuscript from the *Nahuatl* language to Latin. It contains numerous recipes for treating human diseases and 185 colored drawings of the prescribed plants. In 1939 it was first published as "An Aztec Herbarium". However, it also contains XVI century European diseases and medical practices. We present an updated review of this beautiful codex, its history, conception, creators, and botany; as well as, the chemistry and pharmacology of five plants therein cited. The *Libellus* is a window in the time that allows the scientific research of ancient ethnopharmacological knowledge in Mesoamerica and document its persistence, disappearance, or transformation. However, this requires overcoming linguistic defies, but also derived from its historical, anthropological, cultural, botanical, and medical context.

Keywords: American Continent; Mexico; Medicinal plants; Ethnopharmacology; History of science

Resumen: El "*Libellus de Medicinalibus Indorum Herbis*" (Librito de las Hierbas Medicinales de los Indios) fue elaborado por los sabios indígenas Martín De la Cruz y Juan Badiano, 31 años después de la caída del imperio azteca. El primero es su autor, el segundo tradujo el manuscrito del *Náhuatl* al latín. Contiene numerosas recetas para tratar enfermedades humanas y 185 dibujos a color de las plantas utilizadas. En 1939 se publicó por primera vez como "Un Herbario Azteca". Empero, también contiene enfermedades y prácticas médicas europeas del siglo XVI. Presentamos una revisión actualizada de este hermoso códice, su historia, concepción, creadores y botánica; además, la química y farmacología de cinco plantas ahí citadas. El *Libellus* es una ventana en el tiempo que permite la investigación científica del antiguo conocimiento etnofarmacológico en Mesoamérica y documentar su persistencia, desaparición o transformación. Sin embargo, esto requiere superar desafíos lingüísticos, pero también derivados de su contexto histórico, antropológico, cultural, botánico y médico

Palabras clave: Continente Americano; México; Plantas medicinales; Etnofarmacología; Historia de la Ciencia

To the memory of Miguel León-Portilla (1926-2019) and Efren C. Del Pozo (1907-1979)

INTRODUCTION

History, anthropology, and ethnobiology are ways to try to understand the thoughts, knowledge, and life of human beings in the past from different cultures. From another perspective, the information provided by these disciplines has also been used as a starting point for developing new products, such as foods, dyes, fibers, and drugs. Regarding the later, this approach has now been recognized with the Nobel Prize in Physiology or Medicine 2015 granted to Dr. You You Tu for discovering artemisinin, an antimalarial sesquiterpene lactone from *Artemisia annua* (Compositae), a plant named as *"Qing hao"* and recorded almost 1800 years ago in Chinese Traditional Medicine texts (Miller & Su, 2011).

The interest in ancient and current ethnobotanical information, assumed to be generated in good proportion by observation and empirical experience, as a hypothesis for pharmacological and chemical research indeed is not new. Precedents can be found worldwide since the XIX century, or even before, with the investigation of quinine and morphine bearing plants. However, the formal acceptance of ethnopharmacology, ethnobiology, and other related disciplines, in the mainstream Western science can probably be dated to the works of Richard Evans Schultes, Albert Hoffman, and Robert Gordon Wasson in the middle XX century with the entheogen fungi and plants.

This contribution aims to offer an interdisciplinary, holistic, critical, and updated review of the first book of medicinal plants written in the American continent in 1552, the *Libellus Medicinalibus Indorum Herbis* (A Little Book of Indian Medicinal Herbs) (**Figure No. 1**), to promote its investigation and the communication among humanistic, social and natural sciences scholars. We also review the chemistry and pharmacology for some plant species quoted in four recipes, to address the defies for investigating them experimentally. As a hypothesis, it is proposed their medical applications were generated in good proportion by observation and empirical experience, therefore, susceptible to be examined with the scientific method. However, its experimental investigation requires to overcome "translation" challenges not only linguistic, but from its historical, anthropological, botanical, and medical context. The *Libellus* is a real window in the time that allows us to study the persistence, disappearance, and transformation of ethnopharmacological knowledge in Mesoamerica. We finally propose this codex is a copy of an original, now lost.

Figure Nº 1

Left. ***Libellus Medicinalibus Indorum Herbis. f. 1r.*** **Right.** ***Quahalahuac*** **(*Heliocarpus reticulatus* -Malvaceae-),** ***Cihuapahtli*** **(*Montanoa tomentosa* -Compositae-,** ***Quetzalahuexotl*** **(*Salix paradoxa* -Salicaceae-).** ***Recentis partus remedium*** **(Remedy for Recent Parturition).** ***f. 57v.***

History

The *Libellus de Medicinalibus Indorum Herbis* (**Figure No. 1**) was written in 1552 in Mexico, 31 years after the fall of the Aztec Empire (1329-1521) by a coalition of Spaniard soldiers, native enemies, and an epidemic outbreak of the introduced smallpox (*Variola virus*) (Acuña-Soto *et al*., 2002). The *Libellus* author was Martín De la Cruz and was translated from the *Nahuatl* language to *Latin* by Juan Badiano. De la Cruz was a physician, and Badiano a lecturer, in the *Imperial Colegio de Indios de la Santa Cruz de Tlatelolco* (Imperial College of Indians). Both were native scholars in this institution ruled by Spaniard Franciscan priests, adjacent to the Convent of Santiago in Tlatelolco (Somolinos d´Ardois, 1991; Viesca, 1992). Tlatelolco was the sister city of Tenochtitlan, the once center of the Aztec civilization (**Figure No. 2**).

The Colegio was founded in 1536 by Antonio de Mendoza, Viceroy of the New Spain (Mexico), for descendants of native landlords (caciques). The students were admitted into the Colegio at the age of 8-12 years, where they learned Spanish, *Latin*, to read and write *Nahuatl* with alphabetic symbols, as well as, the *trivium* (grammar, logic, and rhetoric) and the *quadrivium* (arithmetic, astronomy, music, and geometry) (Kumate 1992; Cortés 2008; Afanador 2011). The primary purpose of the Colegio was the conversion of students to Christianity, and eventually to prepare them to be priests (Pardo-Tomas, 2013). It was also a way to concoct governors of native communities, meanwhile, the colonial rule was consolidated. "European education, for the indigenous people, especially of noble status, would serve several purposes. On the one hand, well-educated indigenous people would aid research into native languages and polities; on the other hand, they could serve as intermediaries in religious and secular matters. Outnumbered by the natives, Spaniards believed they would benefit from trusted native participation in developing the logistics for better colonization. The moral and intellectual benefits of higher education were also needed to prepare future caciques (lords) to lead Christian communities" (Cortés, 2008).

The Spaniard Gerónimo López, Alderman of Mexico City, wrote in 1541 a letter to King Carlos I of Spain (also Carlos V of the Holy Roman Germanic Empire) and informed him about the education there provided by the Colegio. "It seems it is not enough to teach the natives to write and read, to bind books, to play flutes, chirimías, trumpets and percussion instruments, to be musicians and to know the grammar…they give them so much instruction, and with such care, that there are children that speak Latin with such elegance as Cicerone" (Borgia-Steck 1944; Del Pozo, 1964; Kumate, 1992). The Alderman, instead of praising the educational project, warned on the dangers of preparing native priests, or worst, leaders able to challenge the Spanish rule. Indeed, he also wrote in his letter "The doctrine was good that they learned it; but reading and writing very harmful as is the devil" (Afanador, 2011). In any case, the execution of the *cacique* of Texcoco Don Carlos *Ometochtzin* presumably for idolatry in 1539, who had been educated by Franciscans, "raised serious doubts about the project of instructing the native elite" (Pardo-Tomas, 2013). The funds for the Colegio were suspended in 1541, and a further *"Cocoliztle"* epidemy in 1545 caused the death of many students and Professors, reinforcing the pertinence of closing it. *Cocoliztle* means "disease, plague" (Simeon, 1981). The 1545 epidemy is considered "one of the worst demographic catastrophes in human history" (Acuña-Soto *et al*., 2002). The pathogenic agent probably was *Salmonella enterica subsp. enterica serovar* Paratyphi C (Vågene *et al*., 2018). In 1555 it was published a ban on the ordination of "indios" (natives) preventing to accomplish one of the objectives of the Colegio (Pardo-Tomas, 2013). "Lack of funds owing to growing opposition to the project and a stricter royal administration, among other causes, would contribute to its decline by the 1580s" (Cortés, 2008). However, during 50 years many native intellectuals named *"gramáticos"* (grammarians) emerged from the Colegio and played outstanding roles for preserving their history and ethnical identity through the writing of texts in defense of territorial and genealogical rights, struggling in the framework of the new social, political and legal order imposed by the Spaniard conquest.

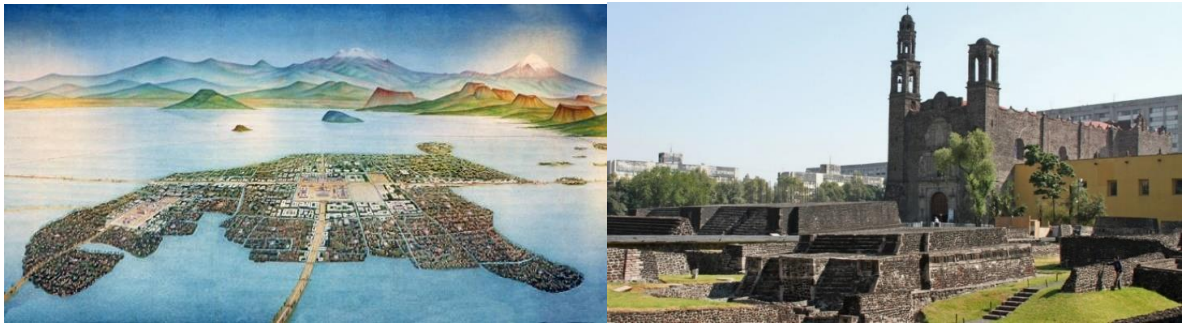

Figure Nº 2
Left. "The Island of México in the XVI Century" by Luis Covarrubias, 1960. Mural at the National Museum of Anthropology, Mexico. Tenochtitlan: central square. Tlatelolco: left rectangle. Right. Tlatelolco. Archeological Zone, Church, and Convent of Santiago

Why was the Libellus ever written?

The most divulged version is that at the beginning of 1552, Jacobo de Grado, the Prior of the Convent of Santiago de Tlatelolco (**Figure No. 2**), asked Martín De la Cruz to compose the *Libellus*. He probably dictated the text in *Nahuatl* to Juan Badiano who translated it to *Latin*, and probably was also the scribe. The *Libellus* was conceived as a present to Carlos I, King of Spain. This to gain the royal favor, and as an appeal to assure the threatened Colegio existence (Somolinos d'Ardois, 1991). The *Libellus* was completed on July 22, 1552, as stated on its last page. It is dedicated to Francisco de Mendoza, son of the former Viceroy and protector of the Colegio. In August or September of that year, Mendoza commanded the naval fleet that left for Spain, taking with him the *Libellus* to accomplish its noble purpose, and it succeeds. A royal decree of May 18, 1553 ordered the new Viceroy Luis de Velasco to provide 800 gold pesos to the Colegio each year until 1558 (Viesca, 1992; Aranda *et al*., 2003).

Viesca (1992) and other historians (Pardo-Tomás, 2013; Abud-Molina, 2015) have explored another hypothesis, more mundane; the *Libellus* was indeed written to support the Mendoza's family business plans. The financial aid for the Colegio in fact arrived on January 9 of 1552 from the former New Spain Viceroy, Antonio de Mendoza (Pardo-Tomas, 2013). By May of that year, his son Francisco asked the Prior Jacobo de Grado to write a "book" to present Carlos I the medicinal repertory from the New Spain. He aimed to obtain a royal license for trading advantageously with spices and medicinal plants produced in the New World to be exported to Europe (Viesca, 1992; Aranda *et al.*, 2003). There is ample documentation on Francisco de Mendoza's arrangements with the Spaniard crown about these trade issues (Abud-Molina, 2015; Rey-Bueno, 2004). Indeed, probably both versions of the *Libellus*' genesis may be complementary.

Martín De la Cruz and Juan Badiano

Until today, we know very little about them. Regarding the author, Martin De la Cruz was probably in his middle or late age by 1552. It has been suggested he entered the Colegio in 1545 to take care of the health of the students during the *Cocoliztle* epidemy. De la Cruz received his Christian name from Friar Martín de Valencia or Friar Martín de Jesús (Guerra, 1952). In New Spain, native physicians attended the native population, but eventually Spaniards. Probably, Martin De la Cruz treated Viceroy Antonio de Mendoza of transient hemiplegia in 1549. As a reward, Mendoza may give him mercy on May 14, 1550, indicating he could have a mule; only Spaniards and important caciques had this privilege. That proclamation also stated De la Cruz was a "principal Indian" born in Tlatelolco (Viesca, 1992).

In 1552 the new Viceroy, Luis de Velasco, signed another document pronouncing Martín De la Cruz, and Antón Hernández as physicians of the Colegio, and indigenous people. Finally, in 1555 the Viceroy authorizes De la Cruz to have and use a crossbow for his protection while being in the fields (Viesca, 1992; Aranda *et al.*, 2003). The author speaks about himself in the first page (**Figure No. 1**) of his masterpiece, as follows: "A little book of Indian medicinal herbs composed by a certain Indian, physician of the College of Santa Cruz, who has no theoretical learning but is well taught by experience alone. In the year of our Lord Saviour 1552" (Emmart, 1940).

In the case of the translator, we know even less. It has been pointed out that he probably was born in 1524, and entered the Colegio as a student in 1536, and was a Lecturer in 1552. He received his Christian name from Friar Juan Badiano, a French Franciscan who carried out the evangelization of the Michoacán province (Guerra, 1952). He wrote about himself in the *Libellus*' last page as follows: "End of the little book of herbs, which Johannes Badianus, an Indian by race, a native of Xochimilco, reader at the same College, translated into *Latin*. Glory be forever to him by whose gift I translated the book you see, good friend reader" (Emmart, 1940).

A long journey to press

After it departed from Mexico in 1552, the *Libellus* started a long journey of nearly four centuries to be published and be known by the world. The survival of this little book is amazement. It is assumed that King Carlos I probably did not know about the *Libellus*, but Prince Felipe II saw it (Somolinos-Palencia, 1990; Somolinos d'Ardois, 1991; Viesca, 1992). However, according to Rey-Bueno (2004), another member of the royal family could have received the Codex. "The truth is that the arrival of Francisco de Mendoza to Spain coincides with the regency of the Infanta Doña Juana, younger sister of the monarch, who oversaw the government of Spain, due to the absence of her father and brother between 1554 and 1559. In fact, Juana established various economic agreements with Francisco de Mendoza, such as his appointment as General Administrator of Mines, or the capitulations related to the trade of medicinal products between the peninsula and the Viceroyalty of New Spain".

Whoever received the *Libellus* in Spain, it remained unknown at the Royal Libraries, until 1623. That year it became the property of Diego de Cortavila, who signed it (*ex libris*), as can be appreciated in **Figure No. 1**. How this royal pharmacist obtained the Codex? One hypothesis goes back to the regency of Doña Juana de Austria from 1554 to 1559. "Juana could well be the depositary of the *Libellus* who, along with other personal belongings of the princess, became the rich artistic legacy of the "Descalzas Reales" (Barefoot Royals), a monastery founded by her; and, perhaps, was another princess of Spain, Nun Margarita De la Cruz, niece of the previous one, who decided to give this codex to her apothecary, Diego de Cortavila" (Rey-Bueno, 2004).

Afterward, Cardinal Francesco Barberini, ambassador of the Vatican in Spain from 1624-1626, became the owner of the codex and he took it to Rome. There, Cassiano del Pozzo, one of Barberini´s diplomatic aides and a member of the *Academia dei Lincei*, ordered to copy it, adding the short title *"Erbe Medicinali del Messico"* (Medicinal Herbs from Mexico) (Guerra, 1952). The *Libellus* remained in the Barberini's Library until 1902, when it was incorporated to the Vatican Library (Gates, 1939; Emmart, 1940; Gates, 2000). The copy was done *circa* 1627 by Vincenzo Leonardi de Grimignano and bought by George III of England in 1762 (Abud-Molina, 2015).

In 1929, the *Libellus* was discovered by Charles Upson Clark and Lynd Thorndike in the Vatican Library. The copy was found by Giuseppe Gabrieli the same year in Windsor, England (Guerra, 1952; Kumate 1992). The importance and artistic beauty of the *Libellus* were recognized, and the works for making it accessible to the public started immediately in the United States, under the auspices of the Johns Hopkins University in Baltimore, USA. In 1939, Professor of Anthropology William Gates published the first translation to English with botanical comments. In 1940, Emily Walcott Emmart published a second translation to English with interesting studies, including those of botany. In the following decades, several attempts were performed in Mexico for publishing the *Libellus*, for instance, that of Guerra (1952) of 200 printed copies (Domínguez, 1969). It contains an introductory study, an etymological index of the plant names, and only 3 drawings. Francisco Guerra was a Professor of pharmacology at the Universidad Nacional Autónoma de México -UNAM- (National Autonomous University of Mexico).

In 1964, the first Mexican *Libellus* facsimile edition was published, accompanied by lore of outstanding studies. Angel Maria Garibay did the translation from *Latin* to Spanish. Garibay was a priest, and the most recognized expert on the *Nahuatl* language of his time, so he also translated the plant names. This publication (De la Cruz, 1964) also included quite interesting studies, ranging from the description of the manufacture of the manuscript, history, art and iconography, botany, zoology, minerals and soils, odontology, medical and documentary value. The botanical interpretations were performed by Faustino Miranda, and Javier Valdés, Professors at the UNAM's Institute of Biology. The editor was Efrén C. Del Pozo (1907-1979). The role of this medical doctor and humanist

was fundamental. Del Pozo performed graduate studies at Harvard University in USA during 1940-1943, where he probably got notices of the publication of the *Libellus* in Baltimore. Afterward, Del Pozo was a Professor at UNAM and occupied leading positions there, and in the Instituto Mexicano del Seguro Social -IMSS- (Mexican Institute for Social Security). This medical institution sponsored the two main Mexican editions of the *Libellus*, but also the experimental research of several plants.

In 1990, Pope John Paul II visited Mexico and brought the *Libellus* as a present to the Mexican people (Kumate, 1992). It was deposited at the library of the Instituto Nacional de Antropología e Historia -INAH- (National Institute of Anthropology and History). To celebrate its return, a second Mexican edition of the *Libellus* was published in two volumes (De la Cruz, 1991). The first containing the facsimile, while the second reprinted the 1964 investigations. In 1992 was published a new book on the *Libellus* by Jesús Kumate, Ministry of Health of Mexico. It contained a novel translation from *Latin* to Spanish by María Eduarda Pineda, new and exciting studies on its history, the European and animal *materia medica*, botany, and the pharmacology of two plants. The botanical study and plant interpretations were performed by Javier Valdés, Hilda Flores, and Helga Ochoterena (1992), Professors at the UNAM's Institute of Biology.

The Libellus

The *Libellus* is organized in thirteen chapters, each page is numbered, and identified as a *folium rectum* (*f. r*) and *folium versum* (*f. v*) in *Latin*, indicating the right or backside of each page, respectively. At the top of each *folium* are written in *Nahuatl* the names of generally one to three plants, below are depicted their figures, and the name of the disease treated with those plants, and finally one, or several recipes (**Figure No. 1**). The first eight chapters are devoted to ailments ordered from head to foot. Chapter 8 also offers treatments for exhaustion, or stress, suffered by governors. Chapter 9 to diseases caused by heat. Chapter to 10 illnesses caused by cold and water. Chapters 11 and 12 are devoted to women (including childbirth), and children, respectively. Finally, Chapter 13 is about the signs of the dying one and the relief of its suffering. Anonymous native artists, probably students of the Colegio, collaborated with their beautifully colored plant drawings, showing a strong influence of Aztec art (Abud-Molina, 2015), but also of European medieval herbals (Hassig, 1989; Afanador, 2011).

The first editions of the *Libellus* emphasized it contained pre-Columbian knowledge, as indicated by the title "The De la Cruz-Badiano Aztec Herbal of 1552" (Gates, 1939) or the Subtitle "An Aztec Herbal" (Emmart, 1940). The editions of 1952, 1964, and 1991 recovered the original title *Libellus Medicinalibus Indorum Herbis*; however, the last two maintained the legend "An Aztec Manuscript". It is now recognized that the *Libellus* written during the Colonial era, is an intercultural product, and includes native and European medical concepts and practices (Viesca, 1992; Bejar *et al*., 2000; Ríos-Castillo *et al*., 2012; De Vos, 2017). Hassig (1989) states: "In spite of the fact that the plants and medicinal recipes described are indigenous, and that their *Nahuatl* names have been retained, the text itself betrays European influence through the inclusion of certain terminology and concepts". These come from the humoral theory of diseases and the doctrine of signatures. Moreover, the *Libellus* was conceived and "shares an important functional similarity with an ancient European manuscript tradition: that of the materia medica, that is as a medical manual". In this context, it includes several diseases that an XVI century European physician could recognize, among others: *Podagra* (Gout, *f. 35v*), *Nigri Sanguinis* (Black Blood, *f. 41r*), *Abdereticam Mente* (Mental Stupor, *f. 53v*) (Emmart, 1940; Viesca, 1992).

On the other hand, the elements of Aztec medicine in the *Libellus* have been studied by Ortiz de Montellano (1975, 1986), López-Austin (1993) and Viesca (1992), within the overall framework of Nahua culture, in which the Aztecs are immersed (León-Portilla, 2005). The health of an individual depended on the balance of three animistic entities, the *tonalli*, the *teyolia*, and the *ihiyotl*. The first inhabited the upper part of the head, associated with the sun and responsible for the heat or life force. The second was in the heart, also produced heat and mostly related to water and rains, and the seat of memory and intelligence. The third was in the liver, connected to the breath and wind, and accounted for strong emotions (Viesca, 1992; Gimmel, 2008).

According to Viesca (1992), in the *Libellus*, the human body displays the structure of the cosmos "Therefore, the tripartite distribution of the universe, starting from the surface of the earth, with the thirteen heavens above, and the nine regions of the underworld is reproduced in the human body from the diaphragm. The supradiaphragmatic regions

correspond to the heavens and those below it, to the underground universe". "Located in a universe that was conceived as acting through an immense series of interrelationships between its various levels, the human being had to maintain a balance of them that meant his health. Celestial influences, hot by nature and those from the underworld, which are cold, should be neutralized…" This is more evident in Chapters 8 and 9, which are dealing with diseases caused by heat, and cold, respectively. The dichotomy reveals a native system of disease classification that can be exemplified by *Contra Cordis Calorem* (For Heat in the Heart *f. 28v*), *Ventris Frigiditas* (Coldness in the Abdomen *f. 32r*). Moreover, Viesca (1992) proposes that the European affiliation diseases in the *Libellus* were incorporated into the native system of classification**.**

Botany & Ethnobotany

Identification, or most precisely taxonomic interpretation, of the plants depicted in the *Libellus* depends mainly on, a) iconography, and b) the names of the plants in *Nahuatl* language (Gates, 1939; Emmart, 1940; Miranda & Valdés, 1991; Valdés *et al*., 1992). Interpretations by the plant drawings are tentative, since these are stylized, and many times not in scale (for instance, trees represented as herbs). The lack of dried specimens impedes observing plant morphology especially that of reproductive organs, and anatomical structures. The place and time of collection in the field are also missing, as well as, the ecosystem, and phenological data necessary for botanical identification (Miranda & Valdés, 1991; Valdés *et al*., 1992; Bye & Linares, 2013a; Bye & Linares, 2013b).

Regarding species interpretation by linguistic means, it has been performed consulting ancient, and contemporary written sources, but mainly by everyday speaking. Indeed, "*Nahuatl*" is a language currently alive in Mexico and Central America. It is the most spoken native language in Mexico, with nearly 1,700,000 persons. The presence of "*Nahuatl*" words or roots in the Spanish spoken in Mexico is evident for naming nature, in toponym, and common duties (Montemayor, 2007). Examples of *Nahuatl* words are *cihua* (woman), *huitztli* (spiny), *pahtli* (medicine), *quahtla* (wild), *quilitl* (edible herb), *xal* (sand), *xocotl* (sour fruit), *yólotl* (heart), *xochitl* (flower). The terms are combined for a full description, for instance: *cihua-pahtli* (women's medicine). The *Nahuatl* plant names after five centuries, have either survived or disappeared, but others have been modified to become a Spanish speaking word, as has been documented by linguists (Montemayor, 2007), and botanists (Martínez, 1979). The role of native people and peasants in preserving the linguistic and ethnobiological heritage has been essential, and in the case of the *Libellus* allows us to compare past and present plant names, their uses, and knowledge.

Despite the difficulties, since its first edition, the *Libellus* has been investigated to interpret the illustrated plants according to modern botanical taxonomy and nomenclature. This task has been accomplished mainly by Gates (1939), Emmart (1940), Recko (1947), Miranda & Valdés (1991), Valdés *et al*. (1992), Bye & Linares (2013a) and Bye & Linares (2013b), who prepared the amplest reviews. These successive works corroborate past interpretations or propose novel ones, this based on linguistic, iconographical, botanical, and ethnomedical arguments. The number of interpreted plants has increased from this cooperative effort through time. Botanical synonymy should be kept in mind since the scientific name of a plant changes with time, and with the taxonomic opinion, therefore, a species can have more than one name.

The *Libellus* quotes 224 plants, 185 of them illustrated, and the remaining 39 mentioned only by their *Nahuatl* names. According to the last review by Bye & Linares (2013a) and Bye & Linares (2013b), until now 131 (71%) of the depicted plants have been identified to species and 17 (9.2%) to genus. The interpreted species of the *Libellus* are a sample of Mexican medicinal flora, estimated at around 3,100 species. At least one of ten plants present in the country are used or have been used, medicinally (Bejar *et al*., 2000; Ríos-Castillo *et al*., 2012).

Interestingly, Valdés *et al*. (1992) noticed plants that are also mentioned in the *Libellus* by their appellations in *Latin*, but are not illustrated, and indicated "could refer to plants that were introduced early to America, or to native plants similar to European ones". In our opinion, most of these denote species from genus common to both the paleoartic and neoartic biogeographic regions of the Earth, such as *Cupressus*, *Pinus*, and *Quercus*. The Spaniard priests surely recognized them akin to those growing in their lands and quite sure instructed Martín De la Cruz about this fact. These are quoted in 11, 8, and 5 recipes, respectively. It is interesting to note that the *Laurus*, surely the Mediterranean *Laurus nobilis* (Lauraceae), is also among the most quoted plants named in *Latin* appearing in 11 prescriptions,

reflecting its medicinal mportance. *Frumento* (wheat) a clearly European introduction into America is mentioned four times.

Besides the *Libellus*, at least two additional treatises deal with the native medicinal plants used in the XVI century in New Spain. The first is the *"Códice Florentino"* (Florentine Codex), also named *"Historia General de las Cosas de la Nueva España"* (General History of the Things of New Spain). It was written during 1540-1585 by the Spaniard Franciscan Friar Bernardino de Sahagún (1499-1590). The second is the "*Historia de las Plantas de la Nueva España"* (History of the Plants of the New Spain). It was written during 1571-1577 by the Spaniard physician and naturalist Francisco Hernández (1514?-1587) (Bejar *et al*., 2000; Pardo-Tomás, 2002; Ríos-Castillo *et al*., 2012).

The *Códice Florentino* also required the active collaboration of the native scholars and students of the *Colegio de Tlatelolco*. The importance of this institution is such, that it has been pointed out that "Tlatelolco was perhaps one of the most emblematic spaces of the circulation of knowledge among people living in sixteenth-century New Spain" (Pardo-Tomás, 2013). Hernández was sent to New Spain by King Felipe II to compilate the medicinal plants and received the title of "*Protomédico General de las Indias, Islas y Tierra Firme del Mar Oceano*" (General Protomedical of the Indies, Islands and Firm Land of the Ocean Sea). He also translated to Spanish the "Natural History" of the Roman *Gaius Plinius Secundus*, Pliny the Elder, (23-79 AD). The history of those texts is also fascinating, and their publication was likewise delayed for centuries (Bejar *et al*., 2000; Pardo-Tomás, 2002; Ríos-Castillo *et al*., 2012).

The *Códice Florentino* quotes 724 plants, 382 of them interpreted botanically (Estrada-Lugo 1989), while the *Historia de las Plantas de la Nueva España* contains 3076 plants, and 1647 interpreted (Valdés & Flores, 1985; Bejar *et al*., 2000; Ríos-Castillo *et al*., 2012). The *Libellus Nahuatl* plant names have been searched and compared with those quoted in the Códice Florentino. Until now this approach has resulted in poor overlap (Del Pozo, 1964; De Vos, 2017). It would be interesting to do this comparison with the interpreted botanical names of the XVI century sources, to circumvent the notable *Nahuatl* linguistic diversity that these texts contain. The more recent interpretations of *Libellus*' plants have focused on understanding the iconographic (Abud-Molina, 2015), and linguistics challenges (Ávila-Blomberg, 2012) for proper botanical identification. The plants' drawings, although influenced by the European canons tending to realism (Abud-Molina, 2015), also contain the principles of knowledge recording in the *Nahua* culture by a painting-orality binomial (León-Portilla, 2003). The pictograms were done by the "*tlahcuiloh*" (painters-scribes) following a code, and their oral interpretation by the *"tlamatini"* (sage) (León-Portilla, 2003). The plant drawings in Aztec manuscripts were also used as mnemotechnic and didactic aids (Del Paso y Troncoso, 1886) for preserving the knowledge through oral tradition. The *tlahcuiloh* were specialists thoroughly trained and worked in the "*calmecac*", an Aztec scholar institution. So naturally, these drawings held the rich metaphorical meaning of Aztec symbols and cosmovision. The finished manuscripts were stored in the "*amoxcalli*" (book-house). Fray Diego Durán (1537-1588), a Dominican friar author of the *"Historia de las Indias de Nueva España e Islas de Tierra Firme"* (History of the Indies of New Spain and Tierra Firme Islands), noticed: "they had all written, drawn in books and long papers with an account of the years, months and days in which it had happened... Their laws and ordinances, their census, with a lot of order and concert". Unfortunately, the proper context on how to analyze these drawings was almost lost after the Conquest, since many of these documents were intentionally destroyed, and only 15 pre-Hispanic Codex survive today.

Abud-Molina (2015) attempting to come up with a methodical process using art history, for investigating the *Libellus*' plant drawings. Her approach was to consider not only morphological features but also several "principles of abstraction" used by *tlahcuiloh*, including "synecdoche, metonymy, and synthesis". Synecdoche refers to the representation of "a part for the whole, or vice versa", for instance, the trunk of a tree as symbolized a branch sticking from the ground. Metonymy is the prevalence of the most striking characteristic of an image, for example, the fruits (**Figure No. 3**). Synthesis is the confluence of several visual elements into one, for instance, an inflorescence or infructescence is seen as a single flower or fruit element in each branch. Finally, pictorial synthesis also concerns with phenology, for instance: flowering and fructification occurring in the same figure, in spite that these events occur at different times. With these principles, Abud-Molina (2015) identified the plant *yztac ocoxochitl* (*f 7r*) as *Pimenta dioca* (Piperaceae), commonly known as "*xocoxochitl*,

pimienta gorda, pimienta de Tabasco", or "allspice", and proposed this was one of the main spices planned to be traded by Francisco de Mendoza when he asked for composing the *Libellus*.

Ávila-Blomberg (2012) recalled the translation of the *Nahuatl* names of the *Libellus*' plants to Spanish have not been reviewed since the Angel Maria Garibay work in 1964. He asserts the need for a new etymological analysis, considering the advances in phonetics, grammar, and lexical composition. The *Nahuatl* plant names express ideas and are more than a word. With this perspective, he reviewed or proposed botanical interpretations for 20 *Libellus'* plants with the aid of current *Nahuatl* plant names, ethnobotanical, and even pharmacological, and chemical data.

The pharmacological and chemical studies

From a natural sciences perspective, the ancient and current ethnobiological and ethnomedical knowledge can be assumed to be generated in good proportion by observation and empirical experience. Adaptative survival of a human population would be favored, for instance, if a remedy is successful, regardless of the interpretation system (magic, religion, or science) used to explain its efficacy. Therefore, ethnomedical knowledge is a hypothesis susceptible to be examined with the scientific method. However, its experimental investigation requires to overcome "translation" defies, not only linguistic, but from its historic, cultural, biological, and medical context.

In the case of *Libellus*, the first step to carry on chemical and pharmacological studies is to have a precise taxonomic interpretation of a quoted plant to a species (Ortiz de Montellano, 1975). In our appraisal, only 30 *Libellus*' plants have consensus about their species identity in the works of Miranda & Valdés (1991), Valdés *et al*. (1992), and Bye & Linares (2013a) and Bye & Linares (2013b). Most of the plants (79) are interpreted to the same species in only two of those reviews. Even if the taxonomic identity of a plant is undisputed, it is necessary a second opening key. That is the interpretation of their ancient medical applications. This, in order to select the pertinent pharmacological model (Derbez *et al*., 1945; Bejar, 1988), to make inferences from the chemical and pharmacological published data, (Domínguez, 1969; Ortiz de Montellano, 1975), or even to perform clinical trials (Terrés, 1894; Lozoya *et al*., 1992). This step can be facilitated when the therapeutic applications of a plant species survive after centuries (Del Pozo, 1966), and its medicinal effects, or pharmacological activity, can be clearly observed.

Figure No. 3
Cihuapahtli* (*Montanoa tomentosa* -Asteraceae-). *f.57v.

To illustrate the "translation defies" of the *Libellus*, in the following sections we review four cases of the XVI century medical traditions here contained, two native, and two European (Viesca, 1992; Bejar *et al*., 2000; Ríos-Castillo *et al*., 2012; De Vos, 2017). We analytically review the quoted ailments, the purported plant species, as well as their chemistry, pharmacology, and the clinical studies when available. The first two cases are plants still used by contemporary peasants and ethnic groups for similar therapeutic applications as those recorded in the codex, such as *Cihuapatli* (*Montanoa tomentosa* -Compositae-) and *Xaxocotl* (*Psidium guajava* -Myrtaceae-). The last two cases are ailments recognized by the XVI century European medicine, such as *Nigris sanguis* (Black Blood) (5.3), and *Abdericam mentem* (Mental Stupor, Stupidity of Mind) (5.4), but treated with native plants. These maladies can be tracked to Greek-Roman times (Hassig, 1989; Viesca, 1992), but are currently unknown in academic and popular medicine.

Cihuapahtli: the women's medicine

After the publication of *Libellus* in 1939 and 1940, one of the first revisited plants was the *cihuapahtli* (**Figure No. 3**). It is quoted in *f.* 57*v* for "*Recentis partium remedium*" (*Remedy for Recent Parturition*). This plant has been interpreted as *Montanoa tomentosa* (Compositae) mainly from linguistics and contemporary ethnobotanical records by Gates (1939), Emmart (1940), and further botanists. Its name derives from the *Nahuatl* words "*cihua*: woman", and "*pahtli*: medicine"; therefore, it is a "women´s medicine". With the time this term was transformed to "zoapatle" in Spanish. It is still used by peasants and native communities in Mexico for child delivery, abortion, and treatment of amenorrhea (Argueta *et al*., 1994). Detailed information to validate pre-Columbian and contemporary use for facilitating child delivery is compiled elsewhere (Bejar, 1985; Bejar *et al*., 2000). This, and other *Montanoa* species, have been thoroughly reviewed chemical and pharmacologically (Lozoya, 1992; Ríos-Castillo *et al*., 2012; Villa-Ruano & Lozoya-Gloria, 2014).

The *Libellus* recipe containing the *Cihuapahtli* (**Figure No. 1**) is quite complex, and states, "If a woman has difficulty in labor, in order to deliver and bring forth the fetus with little effort, she should drink a medicine of the bark *quauhalahuac* tree (*Heliocarpus reticulatus*, Malvaceae), and the herb *cihuapahtli* (*Montanoa tomentosa*, Compositae) crushed in water, the small stone *eztetl* (quartz), with the tail of the small animal called *tlaquatzin* (*Didelphis marsupialis*)" (Emmart, 1940). Plant interpretations are from Bye & Linares (2013b). The other XVI century authors agreed with De la Cruz. Hernández wrote about the *Cihuapatli* in his *"Historia de las Plantas de la Nueva España"* the following*:* "It is hot and dry in third grade, and therefore the infusion or its juice is administered with very good results to delivering women, in doses of two or three ounces, to give birth more easily". Sahagún annotated in the *"Códice Florentino"* how and where occurred the childbirth (Book VI, Cap. XXX). "When the pain oppressed the pregnant one, then they put her in the *temazcalli* (Aztec vapor bath), and when it was time for arriving the newborn, they gave her to drink an herb called *cihuapactli*, shattered and cooked with water";

During the XIX century, the medicine and pharmacy students documented that *zoapatle* was commonly used by the Mexican population, especially for "slow delivery" and carried out their graduating thesis on this plant. José Ramírez compiled in 1895 the clinical, pharmacological, and chemical information available at that time, indicating that *M. tomentosa* was an effective oxytocic, comparable with ergot, and only recommended after the parturition to avoid excessive hemorrhage (Bejar, 1985; Lozoya, 1999). José Ramírez (1852-1904) was a Professor at the "*Instituto Médico Nacional*" (1888-1914) (National Medical Institute) a scientific institution devoted to medicinal plant research. Ramírez also edited the book "*Datos para la Materia Médica Mexicana*" (Data for the Mexican Materia Medica) published in 1895, 1898, 1900, 1907, and 1908, in which XIX century research on medicinal plants are summarized (Morales-Sarabia & Aceves-Pastrana, 2011) including *zoapatle*. In 1929, G. García-Colín reported the isolation of an active oxytocic fraction, presumably an alkaloid. This would lead in the 1930s to the development of a product called "eriocomina" from *Eriocoma tomentosa* (= *M. tomentosa*) by the *Laboratorio Químico Central S.A.* The product was used effectively for several years in clinical practice. Despite this development, the product was abandoned altogether, and publicity against *zoapatle* dangers and misuse as an abortifacient led to discontinuing its use (Bejar, 1985).

In 1945, Derbez *et al*., reinvestigated *M. tomentosa*. In their introduction, these authors reminded the experimental studies done by Professors

of the late *Instituto Médico Nacional* in 1894, and recalled on the past medical experiences, as follows: "Its undoubted clinical activity has always aroused the interest of the physicians, and in Mexican literature are long found articles about its usefulness (Rodríguez, 1869), or dangers (Capetillo, 1894)". Derbez *et al*. (1945) also reminded the eriocomina research done by Ramírez in 1934 on guinea pig and rabbit uterus. They found that an infusion (10:1, 10 mins) of the dried leaves of *M. tomentosa* administered intravenously induced contraction of the *in-situ* uterus of gravid cats, and potentiated the effect of adrenaline; therefore, their results supported the previous reports. Since then *Montanoa tomentosa*, and other species of this genus, were fairly studied chemical and pharmacologically, and even 21 U.S. patents were filled out in 1970-1980. These investigations have been thoroughly reviewed (Bejar, 1985; Lozoya, 1992; Bejar *et al*., 2000; Ríos-Castillo *et al*., 2012; Villa-Ruano & Lozoya-Gloria, 2014).

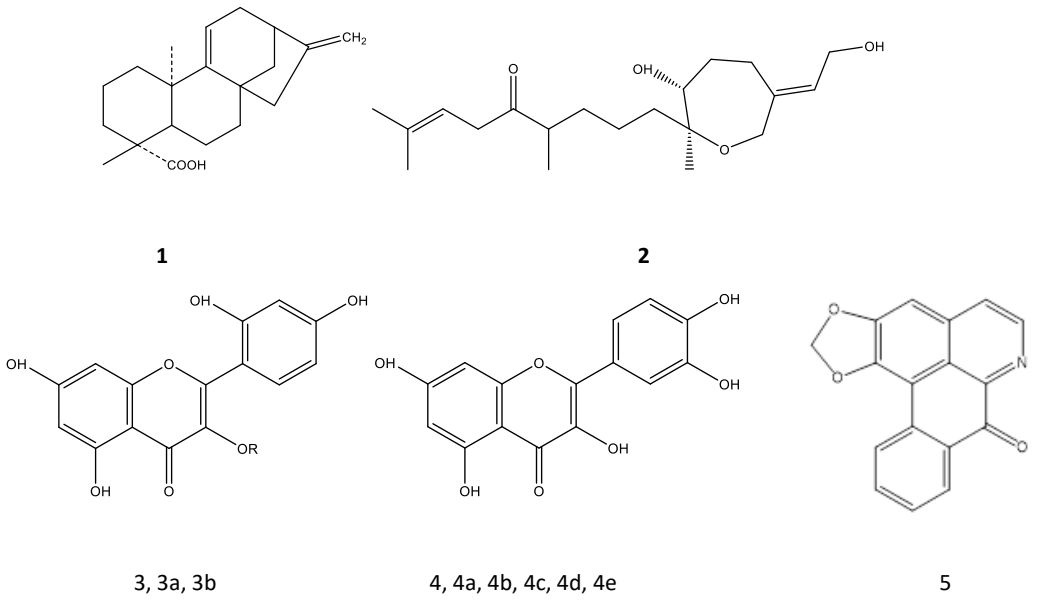

Figure No. 4
***Montanosa tomentosa* diterpenoids: Kauradienoic acid (1), Zoapatanol (2). *Psidium guajava* flavonoids: Morin (3) R = H. Morin derivatives: R = 3-O-α-L-lixopyranoside (3a); R= 3-O-α-L-arabinoside (3b). Quercetin (4). Quercetin derivatives: Guajaverin, R = 3-O- α-L-arabinosyl (4a); Isoquercetin R = 3-O-β-L-glucosyl (4b); hyperin, R = 3-O-β-L-galactosyl (4c); quercitrin, R = 3-O-β-L-rhamnosyl (4d); 3-O-gentobioside-quercetin (4e). *Talauma mexicana* alkaloid: liriodenine (5)**

The main purported active compounds of *Montanoa tomentosa* include diterpenes of the kaurene (kauradienoic acid, kaurenoic acid) and oxepane (zoapatanol, montanol, tomentol, tomexanthin) classes, and their acyclic precursors. The zoapatle aqueous crude extract, kauradienoic acid (= grandiflorenic acid) (**1**), zoapatanol (**2**) (**Figure No. 4**), and analogs are the most consistent and pharmacologically relevant eliciting changes in contractility in animal models and uterus tissue *in vitro*. Kauradienoic acid (**1**) works on uterine smooth muscle by affecting calcium channels and not due to a direct hormonal effect (Bejar *et al*., 1984; Bejar, 1985; Bejar, 1988; Bejar *et al*., 2000).

The volatile constituents of *M. tomentosa* essential oil have also been investigated by gas chromatography coupled to mass spectrometry (GC-MS) being the major constituents borneol acetate, β-cubebene, and β-caryophyllene with 26, 23 and 12%, respectively (Compadre *et al*., 1987). These authors

suggested, but not tested, the possible contribution of toxic monoterpenes, such as borneol acetate, to the alleged antifertility effect of the decoction. Other isolated and characterized compounds include flavonoids, amino acids, sterols, and triterpenes which may contribute to the overall effect seen with the aqueous extract in the popular medical practice. It can be concluded that the effect of the infusion is likely a phenomenon of synergism (Bejar *et al*., 2000).

The research on the uterotonic properties of *M. tomentosa* has diminished in the last years, probably due to a combination of factors, patent disputes, difficulty to pursue clinical trials, and the successful pharmaceutical development of the after-pill emergency contraceptives. The new investigations mainly concern with biological activities not directly related to ancient medical applications. For instance, the anxiolytic and anxiogenic effects of the aqueous crude extract in rats (Estrada-Camarena *et al*., 2019). Scientific ideas advance and separate from history. However, it has been reported that intrauterine administration of the decoction of *M. tomentosa* relieves inflammation of the uterus (postpartum metritis) of dairy cows without altering the ovarian activity; this emmenagogue action was attributed to the oxytocin like properties of the extract at the *corpus luteum* (Ortiz *et al*., 2007). Besides, the oral administration of *M. tomentosa* decoction (50 mg/kg) activated oxytocin producing cells in hypothalamic nuclei, which may be associated with its anti-depressant like effect (Lagunes-Merino *et al*., 2019).

The *Cihuapatli* case illustrates the pertinence of ethnopharmacological knowledge that survives and can be tracked centuries ago and even understood from the Western scientific perspective. However, the *Cihuapahtli* depicted in the *Libellus* still contains mysteries. Its identification has been based mainly on the survival of the plant's name along centuries, but the *Libellus* drawing differs from *Montanoa tomentosa* in the color of the inflorescences and shape of the leaves, so this species interpretation must be taken with reserve (Miranda & Valdés, 1991; Valdés *et al*., 1992). This illustration could probably refer to another species that had the same name in the pre-Columbian times. It is interesting to note, that in the "History of the Plants of the New Spain", Hernández quoted 21 plants containing the *cihuapatli* term along with different appellatives (Ortiz de Montellano, 1975; Bejar *et al*., 2000; Ríos-Castillo *et al*., 2012). Indeed, *Montanoa tomentosa* is the plant that Hernandez named *Cihuapatli hemionitico* (Valdés *et al*., 1985).

Xaxocotl: The guava tree

Psidium guajava (Myrtaceae) (**Figure No. 5**) is another plant currently used in México by peasants, ethnic communities, and popular urban population, for medicinal applications like those recorded centuries ago. Its edible fruits are named "guayaba" and contain numerous small and hard seeds. In English speaking countries it is known as "guava". This tree is native to tropical areas from Mesoamerica, where it was domesticated, but it has been introduced since the XVI century to all the tropics of the world, including Africa, Asia, and India (Díaz-de-Cerio *et al*., 2017). Until today, an infusion of *P. guajava* leaves is used for treating gastrointestinal disorders in México and Guatemala (Cáceres *et al*., 1990; Lozoya, 1992; Argueta *et al*., 1994; Lozoya, 1999; Lozoya *et al*., 2002).

Psidium guajava is named *Xaxocotl* in the *f.* 31*r* of the *Libellus* (**Figure No. 5**). Its name comes from "*xal*: sand, and "*xocotl*: sour fruit (Emmart, 1940). The *xaxocotl* is part of a complex recipe which states: "Are good against the *dysentery*, the leaves of the herb *tlacoamatl* (*Morus* sp, Moraceae), the leaves of *xaxocotl* (*P. guajava*), almond, laurel, bark of almond, of oak, *quetzalaylin* (*Alnus argute*, Betulaceae), *ylin* (*Alnus* sp.), *capulxihuitl* (*Polypodium* sp, Polypodiaceae), and *alectorium* with horn of a deer burned to ashes, with *olli* (latex of *Castilla elastic*, Moraceae) and *frumento* ground up in hot water. The juice is to be taken into the body through the anus by means of clyster of nitre". Plant interpretations are from Miranda & Valdés (1991). Elements of European medicine are *alectorium* (rooster bezoar stone), and *frumento* (wheat, *Titricum* sp.) (Del Pozo, 1964; Lozoya, 1992), but also almond, laurel, and oak (Valdés *et al*., 1992). "In the Spaniard medicine of XVI century, the Greek term *dysenteria* (dysentery) was used to denominate an intestine disease that included abdominal pain, flatulence, colic, and diarrhea, being this aqueous, with mucus or bloody, and accompanied with tenesmus" (Lozoya, 1992).

Psidium guajava or "xaxoxolt" (**Figure No. 5**) is a successful case of historical ethnopharmacology. In this article, we offer an overview of the studies related to its *Libellus* medical applications that lead in Mexico to the development of a phytomedicine to treat gastrointestinal diseases (Lozoya, 1992; Lozoya, 1999; Rivera-Arce *et al*.,

2003; Pérez-Gutiérrez *et al*., 2008). However, it has also been intensively studied in the world for other pharmacological activities thoroughly reviewed (Díaz-de-Cerio *et al*., 2017; Naseer *et al*., 2018). The research related to gastrointestinal diseases started in 1949 with Colliere who tested an aqueous extract of the leaves on *Staphylococcus aureus*, and other microorganisms *in vitro*. This was continued in the following years with other enteropathogenic bacteria, such as *Salmonella enteritidis*, *Bacillus cereus*, and *Escherichia coli*, concluding that the main antimicrobial compounds are morin and its derivatives morin-3-O-α-L-lixopyranosyl (**3a**), and morin-3-O-α-L-arabopyranosyl (**3b**) (**Figure No. 4**) (Colliere, 1949; Rivera-Arce *et al*., 2003; Pérez-Gutiérrez *et al*., 2008). This mixture showed a synergic effect and was enhanced by other flavonoids less potent as antimicrobials, such as quercetin (**4**) and its glycosylated derivatives (**Figure No. 4**). However, these quercetin derivatives are responsible for the remarkable anti-spasmodic and anti-motility properties of the *P. guajava* leaves as reported by an IMSS research group (Lozoya *et al*., 1990; Lozoya *et al*., 1992; Lozoya *et al*., 2002; Rivera-Arce *et al*., 2003).

Figure No. 5
***Xaxocotl* (*Psidium guajava* -Myrtaceae-). *f. 31r*.**

A survey of traditional medicine done in the 1980s indicated that an infusion of *P. guajava* leaves was one of the most common remedies known by the Mexican population for healing gastrointestinal ailments characterized by intestinal colic and diarrhea. The dried or fresh leaves (1-2 g/250-mL water/5-8 mins) were popularly administered orally for 2 to 3 days (3 times/day) (Lozoya, 1992; Rivera-Arce *et al*., 2003). The ethanol and aqueous extracts of *P. guajava* leaves at 80 µg/mL inhibited in more than 70% of the acetylcholine and/or KCl induced contractions of isolated guinea-pig ileum *in vitro*. In addition, the antidiarrheal activity of aqueous and ethanolic extracts of the leaves was demonstrated *in vivo* with mice or rats (Lozoya, 1992).

The IMSS group carried out in 1985 a first clinical study with 320 patients with the acute diarrheic syndrome. The patients experienced reduced intestinal colic, few evacuations, and inflammation two hours after administration of an infusion of *P. guajava* leaves and healed in less than 48 hours (Lozoya, 1992). This group finally achieved to develop a phytomedicine for treating acute diarrheic disease. Its active principles (**Figure No. 4**) were identified as a mixture of several quercetin glycosides: Guajaverin (**4a**); Isoquercetin (**4b**); Hyperin = Hyperoside (**4c**); Quercitrin (**4d**); Quercetin-3-O-gentobioside (**4e**). This was demonstrated with a randomized, double-blinded, clinical study of a phytomedicine containing a standardized concentration of the five glycosylated quercetin flavonoids estimated as Quercetin (**4**) (1 mg/capsule of 500 mg) and administered orally every 8 hours for 3 days to a group of 50 adult patients with the acute diarrheic disease (Lozoya *et al*., 2002). Sustainable harvest of *P. guajava* leaves is now practiced by peasants for manufacturing this phytomedicine registered and marketed in Mexico by

a pharmaceutical company for the treatment of colitis (Arias-Lovillo *et al*., 2009).

The antispasmodic effect and anti-diarrheic capacity of *P. guajava* leaves are related to its content of the Quercetin-derived glycosides (**Figure No. 4**), which are hydrolyzed in the digestive tract releasing Quercetin (**4**). This flavonol is a calcium antagonist agent on smooth muscle fibers and is responsible for the effect of this ancient remedy. Isoquercetin (**4b**) (Quercetin 3-O-beta-D-glucoside) is the principal flavonoid in the leaf with a 32% yield, it notably facilitates the absorption of Quercetin (**4**) in the wall of the small intestine, while the 3-O-Rhamnose derivative (**4d**) is quite inefficient as a Quercetin transporter. The effects of a *P. guajava* leaf extract on the electrolyte and water transport in a secretory diarrhea model has also been described (Rivera-Arce *et al*., 2003).

A review performed from 2004 to 2016 shows an increasing interest in the world on the potential therapeutic applications of *P. guajava* extracts and compounds. For instance, two clinical studies were accomplished for the treatment of menstrual pain and symptoms of diabetes mellitus. Regarding gastrointestinal diseases, numerous pathogens have been tested *in vitro* and less in animal models. Outstanding advances have been achieved on the possible mechanisms of action for controlling infectious diarrhea (Díaz-de-Cerio, 2017). The leaf decoction inhibits the production of the enteropathogenic *Escherichia coli* heat-labile toxin, as well as *Shigella flexneri* cholera toxin. It also blocks their binding to ganglioside monosialic acid, therefore reducing bacterial colonization (both adherence and invasion) to Colon epithelial cell line Hep-2. Besides quercetin, other compounds of *P. guajava* leaves contribute to its antidiarrheal action (Birdi *et al*., 2010). Furthermore, the ethanol leaf extract, along with quercetin, showed maximum antidiarrhoeal activity in a rat subchronic model of diarrhea induced by *Shigella flexneri*. The extract (200 mg/kg) and quercetin (50 mg/kg) reduced the pathogen populations in stools, their water content, and repaired epithelial tissue. They also restored antioxidant status, the expression levels of pro-inflammatory cytokines (IL-6 and TNF-α), along with reactivation of Na^+/K^+-ATPase activity. Docking simulation suggested quercetin inactivates the protease activity of SepA secreted by *S. flexneri* which disrupts epithelial integrity during infection and controls signal cascade (Hirudkar *et al*., 2020).

Figure No. 6
Right: *Cirsium eherenbergii* (Compositae). Center: *Huitzquilitl, Tlatlanquaye*. *Nigri remedium sanguinis* (Remedy for black blood). *f. 41r.* Left: *Peperomia galioides* (Piperaceae)

The Black Blood

The "*Nigri remedium sanguinis*" (Remedy for the Black Blood) is an interesting example of a European ailment registered in the *Libellus* (Hassig 1989; Viesca 1992) which may result in first sight incomprehensible without contextualization. This malady mentioned in *f. 41r* is treated with the native plants "*huitzquilit*", and "*tlatlancuaye*" (**Figure No. 6**). The remedy is prepared as follows. "Both the ground leaves and roots of the herbs *quahtla huitzquilit*, and *tlatlancuaye* are to be cooked in water; to which are to be added a pearl, a wolf liver and our wine. He is to take the juice thus prepared as a drink. Before the mid-day meal, he shall drink another juice pressed from good-smelling flowers of different kinds. He shall walk in a shady place, refrain from venery, drink our wine, moderately, in fact, he should not drink it except as medicine. He shall engage in the very cheerful pursuits, such as singing or playing music and beating the *tympans* which we use in public dancing" (Emmart, 1940).

We interpret this recipe as a treatment against "depression", formerly "melancholy" (Pereña, 1995), based on the following arguments. It is aimed to treat "black blood" which leads to the humoral theory of diseases predominant in the XVI century in Europe (Emmart, 1940; Hassig, 1989; Viesca, 1992). San Isidoro De Sevilla (560-636 AD) (1964), author of "Etymologies" so much appreciated during the Middle Ages, and until the Renaissance, wrote in his "Book IV. On Medicine. Chapter V. On the Four Humors of the Body. 3). All diseases are born from the four humors, namely: blood, gall, melancholy, and phlegm. 5) Melancholy is so-called because it is made up of the blood black sediment mixed with an abundance of gall. The Greeks, call the black *mélan*, and they name the bile *cholé*". This recipe also includes ludic activities, such as singing and playing music, and drinking "our wine" a native fermented beverage made from *Agave* juice. This was then named *octli* and is still currently consumed in central Mexico, but it is now known as *"pulque"*. Emmart (1940) also commented about this disease: "It is to be noted that *melancholia*, as well as *epilepsy* (*f. 51v*) and *mental stupor* (*f. 53v*), were not looked upon as the visitation of an evil spirit but rather as a definitive malady of the body".

Regarding the depicted plants in *f. 41r; Huitziquilitl* (**Figure No. 6**) has been interpreted as *Cirsium ehrenbergi* (Compositae) (Valdés *et al*., 1992; Bye & Linares 2013b). Its *Nahuatl* name means spiny (*huitztli*) edible plant (*quilitl*) (Emmart 1940; Garibay 1991). It is also written in the recipe as *quahtla huitzquilit* indicating it is a "wild" (*quahtla*) or "edible thistle growing in the woods" (Gates, 1939; Gates, 2000). In fact, *C. ehrenbergii* is a tall herb found in the *Pinus* and *Abies* forests in the mountains that surround Mexico City (**Figure No. 2**). Currently, it is known as "cardo" or "cardo santo" (holy thistle), but it is not known as eatable, or for treating "black blood" (Argueta *et al*., 1994). However, *C. ehrenbergii* is used by the *Otomí* ethnia for healing insomnia and *"nervios"* (nerves) (Sánchez-González *et al*., 2008). *"Nervios"* is a folk illness that has been associated with anxiety, and depression (Guzmán-Gutiérrez *et al*., 2014).

Tlatlancuaye (**Figure No. 6**) has been interpreted as *Peperomia galioides* (Piperaceae) (Miranda & Valdés, 1991; Valdés *et al*., 1992; Bye & Linares, 2013b). *Tlatlancuaye* means "jointed stem" (Emmart, 1940), or "which has knees" (Garibay, 1991). It is a small aromatic succulent herb, and indeed has stems with nodes. It grows in the Cloud Forests, outside the Valley of Mexico. Currently, *Peperomia galioides* (**Figure No. 6**) is known in Mexico as "*verdolaguilla*" and used to stop hemorrhages (Aguilar *et al*., 1994). *Peperomia galioides* is used in Ecuador (Wilches *et al*., 2019) for treating "*susto*" (fright). This "cultural illness" is not recognized by academic medicine, it is originated by any "traumatic episode that threatens the physical or emotional integrity of the individual". Symptoms include restlessness, depression, insomnia, anorexia, as well as fever, vomit, and diarrhea (Mata-Pinzón *et al*., 2018).

The anti-depressant like activity can be evaluated by behavioral models in mice with the Forced Swimming Test (Guzmán-Gutiérrez *et al*., 2014; De la Peña *et al*., 2014). Until now, either *Cirsium ehrenbergii* nor *Peperomia galioides* have been investigated for these properties. However, it has been reported that an ethanol extract of *Cirsium japonicum* leaves has antidepressant-like activity at 200 and 400 mg/kg in this model. The active principle is luteolin the majoritarian flavonoid, which shows a dose-dependent effect. It also contains the flavonoids, linarin, pectolinarin, and chlorogenic acid (De la Peña *et al*., 2014). To our best knowledge, only the flowers of *C. ehrenbergii* have been studied chemically detecting the presence of alkaloids in the methanol and hexane extracts (Fernández-Martínez *et al*., 2007). In the case of *Peperomia galioides*, it has been reported the sedative properties of a methanol-water (6:4) extract in mice using the pentobarbital-

induced sleeping time test. The length of sleeping time, but not the onset, was enhanced with 300 and 600 mg/kg. The active principles have not been identified, but this species is known to contain the prenylquinones grifolin, grifolic acid, and piperogalin. The essential oil includes beta-caryophyllene, α-humulene, and epi-α-bisabolol (Wilches *et al*., 2019).

The Yolloxochitl: the heart or the mind flower?

The *Yolloxochitl* (heart-flower) depicted in *folium 53v* (**Figure No. 7**) is another example of the cultural and historical defies for investigating the *Libellus*' plants experimentally. The botanists agree is the tree *Talauma mexicana* (Magnoliaceae) (Miranda & Valdés, 1991; Valdés *et al*., 1992; Bye & Linares, 2013b). A synonym is *Magnolia mexicana*. Its popular name has long suggested it has cardiotonic properties. Indeed, it is the emblem of the "National Institute of Cardiology Ignacio Chavez" founded in 1944. Emmart (1940) annotated: "The *yolloxochitl* is still used today for its medicinal properties. The extract of the petals, leaves, and bark is used for an infirmity of heart… Ramírez reports that extract of the bark is used in the treatment of fevers and it is said to have the same effect on the heart as digitalis..." Emmart quoted José Ramírez in "*Datos para la Materia Médica Mexicana*" (1895). José Terrés, also a Professor of the *Instituto Médico Nacional*, had published in 1894 several reports in the Institute's journal on the benefits on patients of the *yolloxochitl* bark decoction (5 g/140 g water). In September, he found it improved the cardiac function of a patient with cardiac flutter for six days (Terrés, 1894a). In October, he administered the decoction to atheromatous patients at a dose of 5 g per day for six days allowing him to conclude: 1) The preparation increased the pulse width, 2) regulated and retarded the contractions of the heart, 3) if the administration is lengthened, the pulse becomes arrhythmic, as happens with digitalis, 4) after the treatment the effects persisted and even increased if suspended, 5) urine acquired an unpleasant odor, 6) no poisoning was evident at the indicated doses (Terrés, 1894b).

Pérez-Cirera & Roca (1937), Pérez-Cirera & Roca (1938), demonstrated that *Talauma mexicana* extracts from flowers and leaves caused vasoconstriction and a cardiotonic effect when injected to animals. Guerra (1938), also described the same cardiotonic effect. During 1950 to 1966, other researchers would confirm that *T. Mexicana* extracts improve the contraction on ischemic muscle, showing strong cardiotonic activity on the electrocardiograms of cats, in a similar way that other cardiotonic compounds (Pardo *et al*., 1951; Pardo, 1956a; Pardo, 1956b; Del Pozo, 1966). All these studies together supported the ethnomedical applications recorded during the XIX and XX centuries.

Figure No. 7
Yolloxochitl* (*Talauma mexicana,* Magnoliaceae). *f. 53v.

However, the *yolloxochitl* (**Figure No. 7**) depicted in *folium* 53v in the *Libellus* is not directed for an "infirmity of heart", or a similar ailment, but to treat "*Abdericam mentem*", that is "stupidity of mind" (Gates, 2000), or "abderetic mind" (Pineda, 1992), a weird ailment that scientists ignored. Emmart (1940) translated the prescription "*Contra Abderiticam Mentem*" (For Mental Stupor) as follows: "He whose mind is in this condition should drink the juice of the *tlahtlocotic* root crushed in warm water so that he will vomit. A few days later both the bark and roots of the flowers *yolloxochitl* and *cacahuaxochitl* are to be crushed in water; he is to drink the juice before lunch, so that the evil humor lodged in his breast may be rooted out…"*Tlahtlocotic* has been interpreted as the herb *Bidens odorata* (Compositae) (Bye & Linares, 2013a). It is depicted in *f. 27r* for inducing vomit. *Cacahuaxochitl* is recognized as the tropical rain forest tree *Quararibea funebris* (Malvaceae) (Miranda & Valdés, 1991; Valdés *et al*., 1992; Bye & Linares, 2013a).

Interestingly, Emmart (1940) tracked this strange illness *Abdericam mentem*, not to pre-Columbian times, but antique Greece, as she states: "There was a town in Thrace, Abdera, the inhabitants of which had a reputation for folly and stupidity. The adjective *abdereticus*, which Badianus has used here, might, therefore, seem to refer to a state in which the mind failed to function intelligently". D´Harmoville (1842) wrote in his dictionary: "Abderite, inhabitant of Abdera. The Abderites were so stupid, that, even in the days of Cicero, they were said to have abducted mind, mind abdered, or from Abderita, to indicate a gross spirit devoid of any common sense; Abdera was the home of the sophist Protagoras and of Democrito".

Why the *Yolloxochitl*, the "heart-flower" (**Figure No. 7**) was prescribed by a native physician living in New Spain, for the treatment of *Abdericam mentem*, a kind of mental stupor in ancient Greece? León-Portilla (2004) offers clues for unraveling the mystery. In the *Nahuatl* civilization "the heart, *yóllotl*, is associated with cognitive, volitional and creative abilities, and I will add, also associated with feelings…" Elferink *et al*. (1997), which surveyed ancient and modern *Nahuatl* dictionaries, also stated: "The heart is considered as the organ related with mental illness and moods, as results evident from the inclusion of *yollo* (heart) in a considerable number of words which refer to moods or mental illness". These authors recorded nearly 50 *Nahuatl* words related to mental diseases, many with the term *yollo*, such as *yollopoliuhca-yotl*, *yollopoliuliztli* (madness -loss of heart-). Lozoya (1999), asserts *yollotli* damage caused amnesia, loss of wit, fatigue, anger, confusion, oblivion, states deeply and intimately related to changes in vital energy or *tonally*, a *Nahuatl* term meaning force, heat, energy, and that according to the indigenous cosmovision is linked with the sun: *tonatiuh*".

The native translator really overwhelmed the nightmare of Geronimo López, Alderman of Mexico City in 1541, Juan Badiano was learned not only in *Latin* but also in the Greco Roman civilization. Probably, he decided it was more elegant to translate this kind of mental stupor as "*abderiticam mentem"*. Viesca (1992) which surveyed on the Old-world influences in the *Libellus* wrote: "The *mind of Abdera* is a term commonly used by Pliny and other European authors to designate any kind of madness, and is especially used when unreasonableness is added to the conduct not adjusted to the social norms... in this particular case, the hand of Juan Badiano is revealed, or even that of friar Jacobo de Grado, or some other Tlatelolco friar who had certain knowledge of medicine". The "*Yolloxochitl*" illustrates the paradoxes of this beautiful, but challenging manuscript, and reveals crystal clear the importance of accurate cultural translation for the comprehension of the *Libellus*.

The pharmacological properties of *Talauma mexicana* have been reviewed, especially over cardiac functions and blood pressure (Lozoya & Lozoya, 1982; Waizel-Bucay, 2002); but to our best knowledge, it has not been tested to date on the nervous system. The chemical studies of this plant are relatively limited. The presence of an alkaloid, denominated aztequina was initially reported (Sodi-Pallares & Garza, 1948). Collera & Walls (1963) did not find this compound but obtained its essential oil, and isolated costunolide and beta-sitosterol. However, in 1957, Kametani *et al*, following the same procedure as Sodi-Pallares isolated liridonenine (**5, Figure No. 4**) from *Talauma mexicana*.

Liriodenine (**5**) is an oxoaporphine alkaloid, also found in other species belonging to the Magnoliaceae (Chen *et al*., 2013). This alkaloid is an active inhibitor of cardiac Na^+ and Ito (a voltage-gated K^+) channels which may have beneficial effects on antiarrhythmic activity induced by myocardial ischemia (Chen *et al*., 2013). Liriodenine also protects the cardiovascular system under ischemia-reperfusion conditions by preserving the nitric oxide synthase (eNOs) and nitric oxide (NO) production

(Chang *et al*., 2004). The pharmacological effects of liriodenine certainly support the early findings by Terrés in 1894 in a patient with heart flutter, as well as for other studies reported in the 1950s-1960s. The y*olloxochitl* was found to be effective on certain individuals with arrhythmic heart, but not on those requiring a cardiotonic (a positive inotropic effect), like digitalis.

Liriodenine (**5**) has a wide range of other pharmacological activities. Not only shows antibiotic, antiviral, and antiplatelet actions (Chen *et al*., 2013); but it also has effects on the central nervous system (Rios *et al*., 1989; Lin *et al*., 1994). Liriodenine effects on the brain are due to its blockade of dopamine biosynthesis (Chen *et al*., 2013). The dual mechanism of action is the reduction of the enzyme tyrosine hydroxylase (TH) and modulating TH gene expression. It is suggested that the isoquinoline ring planarity plays a key role in the inhibition of dopamine (Chen *et al*., 2013). It also displays an antimuscarinic effect blocking the M3 receptor (Lin *et al*., 1994).

In summary, the native medical applications of *yolloxochitl* became quite obscured after its translation from *Nahuatl* to *Latin*. If *Talauma mexicana* pharmacological research would have focused initially on the original framework of reference of the *Libellus*, its effects on the brain would probably have been demonstrated in several animals and *in vitro* models. Concerning its benefits on the *abderetic mind* mentioned in the *Libellus*, we can only speculate it may show a beneficial tranquilizing effect. This would have to be demonstrated by pharmacological and clinical trials.

A curious work of art or science?

Since its discovering, the *Libellus* has attracted the attention of artists, humanists, and scholars of the social and natural sciences. While its esthetic value is universally recognized, this manuscript has arisen confronted points of view of as a source of information for the different disciplines. Among others: a) for distinguishing the Aztec medicine from the European one, brought during the XVI century (Del Pozo, 1964; Ortiz de Montellano, 1975), b) to explain ancient medicinal applications from the modern chemistry and pharmacology (Del Pozo, 1966, Domínguez 1969; Ortiz de Montellano, 1975), and c) to develop new phytomedicines from this cultural heritage (Lozoya, 1992). Besides the findings exposed in the preceding sections, it is also interesting to know the thoughts, methods, expectancies, and disappointments that experienced those notable researchers while confronted with this beautiful, but challenging manuscript.

In the first Mexican edition of the *Libellus*, Del Pozo (1964) wrote the chapter “Medical and Documental Value of the Manuscript", where he offered a critical point of view, mainly from the perspective of a physician, as he was. He also warned about the "European Contamination in the Manuscript", especially for naming certain diseases, their causes, and treatment. "The *Libellus* can only illustrate about the use of plants in Aztec medicine, but as for medicine itself, the manuscript tells us little… There is only a chapter in which Martín De la Cruz shows an admirable semiology and offers evidence of the results of accumulated and sharp observation. Unfortunately, it is the chapter in which he describes the signs of imminent death. One is perplexed at these pages that seem written by another doctor from who only offer general recipes throughout the book. Again, we regret the absence of the original in *Nahuatl*, where the titles of the diseases identified by the Aztecs, or the detailed description of the symptoms must have appeared in the iterative and rich form of the Mexican language. Juan Badiano went too far in his eagerness to translate the text into *Latin*; Martín De la Cruz resulted quoting Pliny and prescribing wheat and *alectoria*, the rooster bezoar stones".

In his search for the basis of Aztec medicine and therapeutics, Del Pozo (1964) also identified the lines for the experimental research to be practiced in the becoming years and qualified the three main XVI century documentary sources from this perspective. "If Martín De la Cruz is the naive rapporteur, and Fray Bernardino de Sahagún the objective investigator, Francisco Hernández, the *Protomédico* of the Indies, is the learned professional who systematically studied in the sixteenth century the flora and fauna of New Spain, their medicinal properties, but with an intentional detachment from indigenous doctrines, except for the pragmatic information of the healing qualities of their resources… The general comparison of Martín De la Cruz's therapy with that recorded by Sahagún or his informants makes the second appear more rational and devoid of magical elements".

In 1966, Del Pozo published an ample review entitled "Aztec Pharmacology" where he stated: "The weight of old evidence in the general use of a medicinal plant is a good lead for modern research… The way to find the empirical knowledge of Aztec

medicine is to study old evidence and to look for data in faraway places where the Indian population had found refuge". He revised the plants quoted in the *Libellus* with demonstrated pharmacological effects to that date, such as, *cihuapatli* (*Montanoa tomentosa*), *yolloxochitl* (*Talauma mexicana*), *tlalcacapol* (*Karwinskia humboldtiana,* Leguminosae), *toloatzin* (*Datura* spp, Solanaceae). The pharmacological studies, also comprised plants, generally containing alkaloids, quoted in the other main XVI century sources, or in contemporary ethnobotanical records, for instance, *Tzompantle* (*Erythrina americana,* Leguminosae), *cochitzapotl* or *iztaczapotl* (*Casimiroa edulis,* Rutaceae), *yoyotl* (*Thevetia neriifolia,* Apocynaceae). He also included several outstanding hallucinogenic plants then recently investigated, such as *Lophophora williamsii* (Cactaceae), *Rivea corimbosa* (Convolvulaceae) and the well-known entheogenic fungi (*Psilocibe* spp), recorded by Sahagún and Hernández. Therefore, he stated: "Several Aztec plants have justified their old prestige when tested in our present-day laboratories. *Peyotl*, *teonanacatl*, and *ololiuhqui* have been substantiated in modern research as having the same pharmacological properties discovered by the Aztecs".

In 1969, Xorge A. Domínguez, a distinguished Mexican phytochemist, carried out a bibliographic review of the compounds so far isolated and their reported pharmacological activity from plant species interpreted until that date from the *Libellus*, and other XVI century sources. This, as a fast track way to find support to ancient medicinal applications. Domínguez (1969) discerned in his introduction: "The manuscript surprises by the pharmacological findings that the *Nahoas* had achieved. This justifies a comparison of the plants described by these Mexican Indians with the active substances extracted from them". He reviewed 49 species, approximately 13 from the *Libellus*, and the remaining from Sahagún and Hernández. He emphasized these species as a source of pharmacologically active compounds and briefly discussed the chemical and pharmacological pieces of evidence that could support some ancient medical applications. A clear correlation arose from plants then becoming classics of Mexican medicinal plant research, like those previously mentioned (*M. tomentosa*, *T. mexicana*, *K. humboldtiana)*, with the addition of *Tagetes lucida*, and *Senecio canicida* (Compositae). He also remarked about the role of chemotaxonomy as a prognostic tool for the chemistry and pharmacology of unstudied plants.

In 1975, the Professor of Anthropology, and chemical engineer, Bernardo Ortiz de Montellano published the most known worldwide review on the chemistry and pharmacology of the Aztec medicinal plants. His main sources were the works of De la Cruz (1964), Sahagún (1975), and Hernández (1959). His hypothesis that probably can be applied for many other ethnopharmacological investigations in the world was, "Although the religious or magic aspects or Aztec medicine have been greatly emphasized, much empirical research was done by Aztec doctors and their predecessors". Ortiz de Montellano (1975) choose plants "whose botanical identification was agreed on by at least 3 sources". He applied a unique methodology for interpreting chemical and pharmacological data to assess their possible therapeutic efficacy but considering the cultural and historical framework. "The effectiveness should be evaluated in the context of the beliefs of the Aztec informants. For example, the Aztecs believed that fever was caused by interior heat, which could be eliminated by a diuretic, a purgative, or a digestive". He concluded, "If Aztec medicinal herbs are evaluated by standards which take the etiology of disease prevailing at the time into account. Of the 25 plants dealt in this article, 16 could produce most of the effects claimed in native sources, 4 may be active, and 5 do not seem to possess the activity claimed by native informants." In a following work, Ortíz de Montellano (1986) delves into his methodological proposal. He stated that in Aztec medicine "headaches were caused by an excess of blood in the head"; therefore, therapy involved plants "which contain chemicals that are specific irritants to the mucous membranes" and produce sneezing and nosebleeds (Ortiz de Montellano, 1975; Ortiz de Montellano, 1986). With this approach, the "indigenous treatment of headaches is 90% successful… Whether these same plants were assessed by Western biomedical standards, only 30% would be effective or possible effective" (Ortiz de Montellano, 1986).

The publication of the second *Libellus* Mexican facsimile edition in 1991 allowed its ample diffusion. As previously mentioned, this edition was followed by a new book (Kumate, 1992) containing several studies. The physician and scientist Xavier Lozoya (1992) contributed to the pharmacological review of *Cihuapatli* and *Xaxocotl* since the XVIII century to 1990. There, he also expressed his disappointment with the appraisal of the codex by the

national medical community. "The pharmacological study of the plants described in the *Libellus de Medicinalibus Indorum Herbis* has been a sporadic task performed in Mexico by a few scientists, and only recently appreciated by Mexican Medicine… during almost half a century it was perceived only as a curious work of art; a beautiful sample of the magical sight that the representatives of the *Nahua* medical culture inherited us, but lacking scientific interest."

Discussion

The "*Libellus Medicinalibus Indorum Herbis*" is also known as "*Codex De la Cruz-Badiano*" (Gates, 1939) or "*The Badianus Manuscript*" (Emmart, 1940). The last two titles properly highlight the role of the translator, not only from the linguistic perspective but conceptually. Certainly, the author did not have a way to approve the translation, and Del Pozo (1964) was perplexed about the "European contamination" and wrote, "Badiano went too far". Translator, traitor? Gimmel (2008) stated about Badiano's role: "perhaps should be considered a co-author of the text who modified it appeal to a European audience?... If De la Cruz was the *tlamatinime* or sage, then Badiano was the scribe who interpreted his spoken words alphabetically adding his own views and knowledge" (Gimmel, 2008).

It should not be forgotten that Martín de la Cruz, Juan Badiano, friars, Professors, and students of the *Imperial Colegio de Indios de la Santa Cruz de Tlatelolco* were all subjected to a despotic power system. Rights as the freedom to express and write personal points of view were limited in that society, even for learned Spaniards. Sahagún suffered censorship, seize of his works, and animadversion of his countrymen for recording a vanishing world. In the struggle for the survival of the Colegio, the "European contamination" of the *Libellus* (Del Pozo, 1964) seems logical and necessary to demonstrate the intellectual and artistic abilities of the Professors and students and its successful acculturation. Therefore, the manuscript was conceived to look as a European herbal that evidenced an ample knowledge of the acquired culture, including quotes to Pliny and to ailments such as *Aberetic Mind* and *Black Blood*, rational for a physician of those times. "Probably it is the last great medieval herbarium" (Somolinos d'Ardois, 1991).

However, the *Libellus* has also been suggested as a product of cryptic cultural resistance, (Viesca 1992; Cortés, 2008); or resilience, taking advantage of a permitted way to leave a testimony. "The Codex De la Cruz Badiano illustrates the ability of indigenous inhabitants to appropriate European forms to their own ends, even when seemingly conforming to European traditions and theories… Just as Europeans reading the Codex would see references to humors and sympathetic medicine, so too would the indigenous readers of European texts have seen references to humors as examples of the imbalance of the *tonalli*, *teyolia*, and *ihiyotl*" (Gimmel, 2008).

Regarding the *Libellus* itself, many issues are still a mystery. Del Pozo (1964) wrote, "we regret the absence of the original in *Nahuatl*". Did it exist? Guerra (1952) suggested that at least a draft was surely available for guiding the elaboration of a manuscript to be offered to the king. Gimmel (2008) also stated, "We must infer that the translation was from an original *Nahuatl* text, composed or, more likely, dictated by the indigenous doctor De la Cruz. Unfortunately, that original if it ever existed, has disappeared". We support this original may have existed from the following arguments: a) the time to elaborate *de novo* the *Libellus* was too short for collecting 187 plants alive and to write about them, but enough to copy the drawings and to make a linguistic and cultural translation, b) several plant illustrations exhibit different stages of phenology, therefore were collected at different times of the year and then fused following the "synthesis" concept (Abud-Molina, 2015), c) many of the recorded species thrive in distinct and far ecosystems, no way a "walking distance" from Tlatelolco.

Martín de la Cruz stated on the first page he composed the *Libellus* in 1552 (**Figure No. 1**), and Juan Badiano announced on the last page it was finished on the holy day of Saint Mary Magdalene (July 22) of the same year. That means at most seven months. It is also known the urgency, and haste of Francisco de Mendoza to have the document (Somolinos d'Ardois, 1991; Viesca, 1992), so the available time could have been even less. This might explain why the *Libellus* seems to not be corrected by a friar expert in *Latin* (Somolinos d'Ardois 1991), or why some *folia* are empty, or with a blank space at the right side as if a missing plant was to be drawn there (**Figure No. 1**). Therefore, the *Libellus* is probably an unfinished manuscript and a copy.

It has been estimated that 60% of the drawn *Libellus*' plants thrive in the Valley of Mexico (Valdés *et al*., 1992), where Tlatelolco is located (**Figure No. 2)**. This endorheic basin comprises

elevations from 2200 to 5445 meters above sea level (m.a.s.l.). Ten different plant communities can be found here (Rzedowski, 2005), among them: aquatic vegetation, grasslands, *Senecio*, and xerophytic shrublands (2200-2400 m.a.s.l), as well as, forests of *Quercus*, *Pinus*, and *Abies* at the surrounding mountain ranges (2300 to 3500 m.a.s.l.). Today only remnants survive of the once great lakes, and of the natural vegetation that grew at the lowest altitudes. The most preserved are the forest ecosystems in the mountains. However, several *Libellus'* plants can be found "nearby" even today to Tlatelolco (<15 Km); for example, *Montanoa tomentosa* (**Figure No. 1 and Figure No. 3**) grows in a protected *Senecio* shrubland inside Mexico City. Though, in 1552 it would require a walking trip of several days to get species of the *Pine* and *Abies* forests, such as *Cirsium eherenbergii* (**Figure No. 6**). Other plants, such as *Psidium guajava* (**Figure No. 3**) flourish outside the Valley of Mexico at the Tropical Deciduous Forests. Only 100 km away from Tlatelolco, but it is needed to ascend to 3000 and then descend to 1000 m.a.s.l. More time would require collecting *Peperomia galioides* (**Figure No. 6**) and *Talauma mexicana* (**Figure No. 7**) from Mesophyll Forest (1500 m.a.s.l.), without speaking of species from the Tropical Rain Forests, close to the sea level, 450 km distant. Hence, the *Libellus'* plant drawings could be more easily copied from a codex, now lost, considering the available time, as well as, the geographical and phenological difficulties to collect them.

It can also be thought-about complementary alternatives. Some plants could be already cultivated at the orchard of the Convent of Santiago Tlatelolco, or at the *chinampas*, a sort of aquatic agroecosystems considered "floating gardens" or found as weeds in the crop fields. Of course, many other plants could be brought by merchants to the famous native market of Tlatelolco, but quite sure most of them dried. In fact, this city was well-known in the pre-Hispanic times for its medical tradition (Viesca, 1992) possibly due to this facility.

The soundest option could be the once notable Aztec botanical gardens associated to the royal palaces. These preserved medicinal and aromatic plants, highly esteemed introduced species, such as the tree *Talauma mexicana*; but also, water resources, birds, and all sorts of animals (Del Paso y Troncoso, 1886; Rodríguez-Figueroa, 2018). Unfortunately, after the conquest in 1521, these gardens were abandoned or intentionally destroyed by Spaniards (Clavijero, 1853; Morales-Folguera, 2004). Nevertheless, the *Oaxtepec* tropical garden hardly survived as part of the Hospital founded there in 1556 by Saint Hippolytus' ordained friars (Lascurain, 2010). The final possibility could be murals. Del Paso y Troncoso (1886) noticed that Clavijero (1853) wrote the following referring to the poet king *Nezahualcoyotl* (1402-1472) of Texcoco: "He devoted himself to the knowledge of plants and animals, and since he could not have in his court those proper of a different climate, he got lively painted in his palaces all the plants and animals of the land of Anahuac: famous Doctor Hernández witnessed these paintings, he saw them and partially used them". Certainly, thorough historical investigations are needed to know the state of conservation in 1552 of the formerly outstanding Aztec botanical gardens, the royal palaces murals, and the commercial activity of Tlatelolco.

The *Cihuapatli* (*Montanoa tomentosa*) and *Xaxocotl* (*Psidium guajava*) in the *Libellus* illustrate the pertinence of ethnopharmacological knowledge that survives and can be tracked centuries ago and tested as a hypothesis from the Western scientific perspective. However, certain maladies, such as *Nigris Sanguis* and *Abdericam Mentem* from European XVI century medicine have been forgotten by popular and academic medicine, as well as by experimental researchers. Why? Probably, because these are referred to treat diseases, that currently can only be comprehended knowing its cultural and historical context. The same may occur with certain ailments from the Pre-columbian medical tradition, such as *Fulminis Ictum* (For Lightning Stroke *f. 50 r*), *Contra Cordis Calorem* (For Heat in the Heart *f. 28v*), *Ventris Frigiditas* (Coldness in the Abdomen *f. 32r*). Comparative studies could enlighten on the persistence or disappearance of these concepts in the current ethnomedicine. Many *Libellus* recipes also include minerals, gems, animal parts, blood, or urine, ingredients probably only understandable based on magic or religious thinking. Ortiz de Montellano (1975) stated: "The medicinal concepts of the Aztecs at the time of the Spanish Conquest were a mixture of magic, religion, and science"; but this statement is also valid for the European medicine at that time (Hassig, 1989). The epistemology of ancient knowledge is certainly a long and winding road.

CONCLUSIONS

The *Libellus* is a real window in the time that allows us to study the persistence, disappearance, and transformation of ethnopharmacological knowledge

in Mesoamerica. We propose this codex is a copy of an original, now lost. It shows the convergence of XVI century New and Old-world medicinal concepts and practices in New Spain, with the native plants as therapeutic elements. The information provided by the *Libellus* is susceptible to be examined experimentally with the scientific method. This approach has been successful for those plants whose medical applications survived after centuries and that can be observed without too much interpretation. In other cases, understanding the quoted medical applications requires to overcome "translation" challenges, not only linguistic, but from the historic, cultural, botanical, medical, and pharmacological perspectives.

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PHOTOGRAPHIC CREDITS

Figure No. 1

Libellus Medicinalibus Indorum Herbis. f. 1r. & *f. 57v.* by INAH (Instituto Nacional de Antropología e Historia. México).

Figure No. 2

The Island of México by Luis Covarrubias, 1960. **http://www.mexicomaxico.org/Tenoch/TenochD.htm**.

Tlatelolco by Gengiskanhg, ca. 2008. **https://www.artchitectours.es/tour/tlatelolco-mexico/**

Figure No. 3

Cihuapahtli. Libellus Medicinalibus Indorum Herbis f. 57v. by INAH. *Montanoa tomentosa* by Ricardo Reyes-Chilpa.

Figure No. 5

Xaxocotl. Libellus Medicinalibus Indorum Herbis. f. 31r. INAH. Fruit of *Psidium guajava* (Myrtaceae) by Xochitl Amancio in Naturalista.mx. Flower of *Psidium guajava* (Myrtaceae) by Asep Suwandi in Pexels.com.

Figure No. 6

Cirsium eherenbergii -Compositae- by Pedro Tenorio-Lezama in plantae mexicanae tenorianae. *Libellus Medicinalibus Indorum Herbis f. 41 r.* by INAH. *Peperomia galioides* -Piperaceae- by Sandra Elena Mansilla-Romeu.

Figure No. 7

Libellus Medicinalibus Indorum Herbis. f. 53 v. by INAH **Right:** Flower of *Talauma mexicana* (Magnoliaceae) by Pedro Tenorio-Lezama in plantae mexicanae tenorianae. Fruit of *Talauma mexicana* (Magnoliaceae) by Reyna Osuna-Fernández.

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