

République Algérienne Démocratique et Populaire
Ministère de l'enseignement supérieur et de la recherche scientifique
Université Abderrahmane Mira-Bejaia
Faculté des sciences de la nature et de la vie
Département de biologie physicochimique

Mémoire de fin de cycle

En vue de l'obtention du diplôme de Master
Option : génétique fondamentale et appliquée

Thème

***Etude épidémiologique de l'hémoglobine glyquée chez
des patients atteints de diabète de type 2***

Réalisé par:

AZZEGGAH Yousra & HOUANTI Nadjette

Membres de jury:

Promoteur: Mr **ATMANI Djebbar**

Présidente: Mme **Ouahmed BOUDAOUH Hania**

Examinatrice: Mme **DEBBACHE BENAIDA Nadjette**

Date de soutenance: **19 septembre 2021**

1. Page de garde de mémoire de Master

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جامعة بجاية
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Université de Béjaïa

Faculté des Sciences de la Nature et de la Vie
Département Biologie Physico-Chimique
Laboratoire de Biochimie Appliquée

THÈSE
EN VUE DE L'OBTENTION DU DIPLOME DE
DOCTORAT

Domaine : Sciences de la Nature et de la Vie Filière : Sciences Biologiques
Spécialité : Biochimie Appliquée et Biotechnologies

Présentée par
AISSAT Aghiles Karim

Thème

**Dosage des composés phénoliques et évaluation des activités biologiques
des fruits de *Pistacia lentiscus* en fonction du stade de maturation**

Soutenue le :

Devant le Jury composé de :

Nom et Prénom	Grade		
Mr TOUATI Abdelaziz	Professeur	Univ. de Bejaia	Président
Mr ATMANI Djebbar	Professeur	Univ. de Bejaia	Rapporteur
Mr RICHARD Tristan	Professeur	Univ. de Bordeaux	Co rapporteur
Mr HABA Hamada	Professeur	Univ. de Batna 1	Examineur
Mme CHAHER-BAZIZI Nassima	MCA	Univ. de Bejaia	Examineur
Mme DEBBACH-BENAIDA Nadjet	MCA	Univ. de Bejaia	Examineur
Mr VALLS FONAYET Josep	MCA	Univ. de Bordeaux	Invité

Année Universitaire : 2021/2022

2. Page de garde de thèse de doctorat



Original Article

Hepatoprotective and antidiabetic effects of *Pistacia lentiscus* leaf and fruit extracts



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ABSTRACT

Pistacia lentiscus (Anacardiaceae) is commonly used in folk medicine to treat various diseases. The aim of the present study was to evaluate the hepatoprotective and antioxidant activities of extracts of *P. lentiscus* leaves (PL) and fruits (PF) against experimentally induced liver damage. Furthermore, characterization of extracts was attempted by a spectroscopic methodology (Fourier transform infrared spectroscopy) and high-performance liquid chromatography with diode array detection analysis. A hepatoprotective potential against paracetamol [165 mg/kg body weight (b.w.)] toxicity was noticed in mice pretreated with the same dose of PL or PF extract (125 mg/kg b.w.) or a combination of both (PL/PF 63/63 mg/kg b.w.), as revealed by an analysis of biochemical parameters (alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities and total bilirubin). These results were confirmed by histological examination of the liver, which revealed significant protection against paracetamol-induced hepatic necrosis. Furthermore, PF extract exhibited a promising antidiabetic activity in streptozotocin-induced diabetic rats, similar to the reference drug glibenclamide (0.91 g/L), a result confirmed by *in vitro* inhibition of α -amylase. We demonstrated that the leaf crude extract showed the best effect in all tested methods, compared to its fruit counterpart, probably due to the presence of higher amounts of phenolic compounds, as determined by phytochemical and Fourier transform infrared spectroscopy analyses. Moreover, high-performance liquid chromatography with diode array detection led to the identification of six compounds for each part of the plant. Gallic acid, a characteristic compound of *Pistacia* species, was most abundant in leaves and fruits, while luteolin was detected for the first time in fruits. Obtained activities of *P. lentiscus* extracts may well be due, at least in part, to the presence of the above compounds.

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3. Première page d'un article scientifique (Article original)

Identification of bioactive compounds from *Fraxinus angustifolia* extracts with anti-NADH oxidase activity of bovine milk xanthine oxidoreductaseNadja AHMANE¹, Dina ATMANI-KILANI¹, Nassima CHAHER¹, Karima AYOUNI¹, Meriem RAHMANI-BERBOUCHA¹, Grégory DA COSTA², Nadjat DEBBACHE-BENAIIDA¹, Tristan RICHARD², Djebbar ATMANI^{1*}
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Abstract: *Fraxinus angustifolia* leaves and bark are used in traditional medicine against various inflammatory-related pathologies incubent to reactive oxygen species (ROS) generation by the NADH oxidase activity of enzymes such as xanthine oxidoreductase (XOR). This study was designed to investigate the in vitro and in vivo inhibitory activities of this enzyme by *Fraxinus angustifolia* extracts. The leaf organic phase of ethyl acetate (LFA) and its bark aqueous counterpart (BFA) showed the strongest anti-NADH oxidase activity in vitro ($IC_{50} = 38.51$ and $42.04 \mu\text{g mL}^{-1}$, respectively). They consequently suppressed superoxide generation both enzymatically (53% and 19%, respectively) and nonenzymatically (34% and 19%, respectively). These results were corroborated in vivo, with high anti-NADH oxidase potential of the leaves and bark extracts (75.32% and 51.32%, respectively) concomitant with moderate hypouricemic activities (36.84% and 38.59%, respectively). Bio-guided fractionation led to the identification, by LC-DAD-MS/MS, of esculin and calceolariside in bark and kaempferol glucoside in leaves as the main compounds responsible for the anti-NADH oxidase activity of XOR. These results plead in favor of the use of *F. angustifolia* as a source of potentially interesting therapeutic substances.

Key words: *Fraxinus angustifolia*, NADH oxidase, xanthine oxidoreductase, phenolics, hyperuricemia

1. Introduction

Xanthine oxidase (XO) and xanthine dehydrogenase (XDH) are interconvertible forms of the same enzyme, known as xanthine oxidoreductase (XOR). In a mammalian fresh tissue, XOR exists under the XDH form, which is NAD-dependent and produces primarily NADH at the FAD site (Waud and Rajagopalan, 1976; Hattori, 1989). However, this form is easily converted to an O_2 dependent type (XO) during the procedures of extraction and purification. Both forms of the enzyme show NADH oxidase activity, with generation of ROS, but XDH is somewhat more effective in this respect (Atmani et al., 2005). In milk, the physiological function of xanthine oxidase has long been a puzzle, but it turned out to play an antimicrobial defensive role in the neonatal gut because of ROS generation (Harrison, 2005). The secretion of milk fat globules is another useful task of the enzyme in a process dependent on the enzyme protein rather than on its enzymic activity (Harrison, 2006). In liver and intestine, ROS species are directly produced by XOR, with uric acid as its end product, whereas they are generated secondarily by XDH, as the enzyme produces primarily the reduced

β -nicotinamide adenine dinucleotide (NADH) (Sanders et al., 1997; Vorbach et al., 2002). In this case, an increase is observed in NADH concentration and the generation of O_2 and H_2O_2 is greatly amplified (Maia et al., 2007). It has been demonstrated that these ROS species are involved in the genesis of pathologies such as alcoholic hepatotoxicity (Teplava et al., 2017) and ischemia-reperfusion injury (Granger et al., 2001). Additionally, simple upregulation of XOR activity, irrespective of XDH/XO ratios, could well be triggered either by hypoxia or by pro-inflammatory agents, implying a strong link of the enzyme with inflammation (McCord and Roy, 1982; Cantu-Medellin and Kelley, 2013). Hyperuricemia could also be generated by a high XO/XDH activity, causing an accumulation of uric acid crystals in joints with the ultimate development of gouty arthritis characterized by an inflammatory leukocyte response (Haskard and Landis, 2002). Hence, the inhibition of XO/XDH will contribute to the healing of this disease.

Numerous studies were directed towards seeking powerful natural inhibitors of xanthine oxidase (Berboucha et al., 2009), but much less attention was given

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4. Première page d'un article scientifique (Research article)

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Université A. Mira de Bejaia

Faculté des Sciences Médicales
Département de Médecine



GENETIQUE

DU CARACTERE AU GENE

Polycopié destiné aux étudiants des tronc communs
Médecine et Sciences de la Nature et de la Vie

Elaboré par

Dr Djebbar Atmani
Maître de Conférences

2008/2009

Ministère de l'Enseignement Supérieur
et de la Recherche Scientifique

Comité National d'Evaluation et de Programmation
de la Recherche Universitaire

**PROPOSITION DE PROJET DE
RECHERCHE EN BIOLOGIE**

Intitulé

**ETUDE DES PROPRIETES ANTIOXYDANT ET
ANTI-RADICALAIRE DES EXTRAITS DE
Fraxinus angustifolia ET *Pistacia lentiscus***

Structure de rattachement:

- Département de Biologie Physico-chimique
- Faculté des Sciences de la Nature et de la Vie
- Université Abderrahmane MIRA, Bejaia

Année : 2006

Ministère de l'Enseignement Supérieur et de la Recherche Scientifique
Université A. Mira de Béjaia
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Spécialité : Biologie

Domaine de recherche : Biochimie des substances naturelles

Bilan Annuel/ 2012

Numéro de code du Projet : F00620100006

Intitulé

**ACTIVITE BIOLOGIQUE IN VITRO ET IN VIVO DES
EXTRAITS DE FRAXINUS ANGUSTIFOLIA ET DE
PISTACIA LENTISCUS**

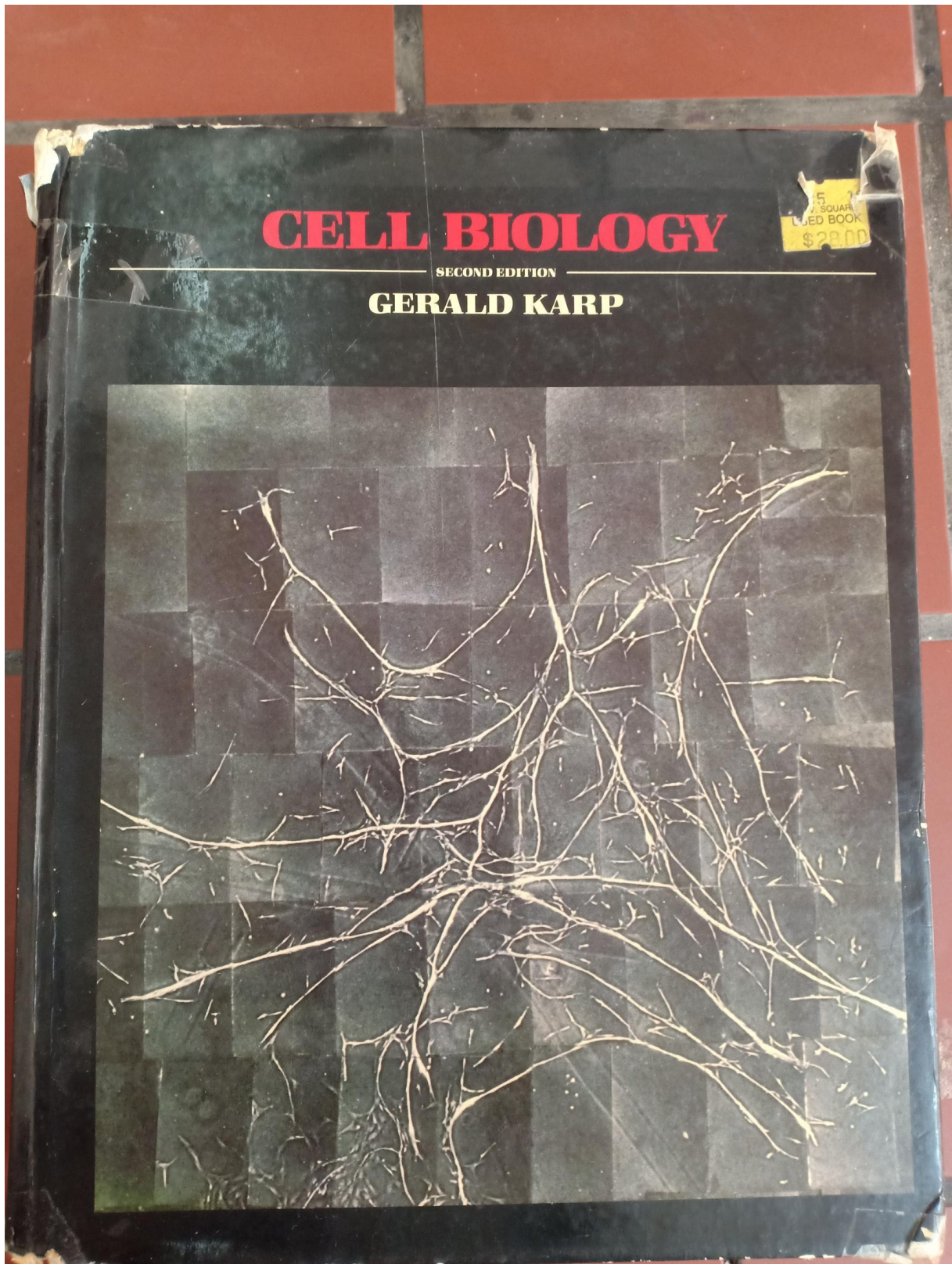
Responsable du Projet

ATMANI Djebbar : Professeur, Directeur de Recherche

LISTE DES CHERCHEURS ET EMARGEMENTS

Noms et Prénoms	Grades académique	Grades de recherche
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AYOUNI Karima	Maitre assistante A	Chargée de Recherche
RAÏMANI Meriem	Maitre assistante A	Chargée de Recherche
CHAHER Nassima	Maitre assistante A	Attachée de Recherche
DEBBACHE Nadjet	Maitre assistante A	Chargée de Recherche

7. Page de garde d'un bilan d'activité de projet de recherche



8. Page de garde d'un ouvrage édité destiné aux enseignants et aux étudiants