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THEME

Antioxidant properties, prebiotic effect and intestinal protection of wheat and barley enriched diets in male Wistar rats

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To my wonderful parents, whose constant love, support, and encouragement have been my most powerful source of strength. A special thank you to my mother for her unwavering support and belief in me. This accomplishment would not have been achieved without your sacrifices and belief in me.

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Dedication

To the mountain on which I always leaned, my dear father, And the watchful eye my mother is the great supporter and the artery of my heart, to my sisters, to myself, to my teachers, to my best friends, to all of who coexisted and shared us moments of happiness and sadness within this great edifice, the University of Echahid Hamma Lakhdar, to all loves, I dedicate this achievement.

MOKRANI Nour Elhouda

Dedication

And the last of their call will be; Praise to Allah, Lord of the worlds

To the one who raised me, my caring mother may Allah save her

To my dear father, may Allah have mercy on him

To my dear brothers, may Allah protect and protect them

To my dear friends

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NAMOUSSA Karima

Abstract

The purpose of this study is to evaluate the influence of wheat and barley-derived prebiotics on gut microbiota and health parameters in Wistar rats. Wheat (Triticum aestivum) and barley (Hordeum vulgare) were selected as prebiotics and harvested in the El Oued region. The study assesses the in vivo biological effects of a diet rich in wheat and barley. Male Wistar albino rats were fed a diet comprising 30% prebiotics (wheat and barley) and 70% mabroma for two weeks.

We assessed malondialdehyde (MDA), glutathione (GSH), and catalase (CAT) activity in the liver, kidneys, brain, and blood, as well as conducted histological examinations of the colon and bacterial analysis. In rats fed a wheat and barley diet, MDA levels, as well as CAT and GSH activity, were notably higher than in controls. For instance, the brain exhibited greater MDA levels for wheat, barley, and wheat-barley combination groups (4.32±0.44 µmol/l), (4.37±0.76 µmol/l), and (4.29±0.28 µmol/l), respectively, compared to the normal group (2.47±0.89 µmol/l). Additionally, the wheat group rats had a higher MDA level in their blood (3.73±1.37 µmol/l) compared to the normal group.

Regarding GSH, all values were high, even for the control group. For example, the wheat group (2.37±0.38 µmol/mg) and barley group (2.30±0.27 µmol/mg) had higher kidney values than the normal group (2.27±0.21 µmol/mg). Histological study revealed that treated rats had thicker colons with a significant increase in total wall thickness in the colon of rats fed on wheat+barley (258.80µm) and barley (192.77µm) compared to the normal group (133.32µm), with differences of 125.48µm and 59.45µm, respectively. Additionally, beneficial microorganisms such as Leuconostoc mesenteroides were discovered.

Thus, our data show that wheat and barley prebiotics improve colon thickness, exhibit antioxidant effects, and positively influence gut microbiota and health parameters in vivo.

Keywords: prebiotics, wheat, barley, biological activities, gut microbiota.

Résumé

Le but de cette étude est d'évaluer l'influence des prébiotiques dérivés du blé et de l'orge sur le microbiote intestinal et les paramètres de santé chez les rats Wistar. Le blé (Triticum aestivum) et l'orge (Hordeum vulgare) ont été sélectionnés comme prébiotiques et récoltés dans la région d'El Oued. L'étude évalue les effets biologiques in vivo d'un régime riche en blé et en orge. Des rats albinos Wistar mâles ont été nourris avec un régime comprenant 30 % de prébiotiques (blé et orge) et 70 % de mabroma pendant deux semaines.

Nous avons évalué les niveaux de malondialdéhyde (MDA), de glutathion (GSH) et l'activité de la catalase (CAT) dans le foie, les reins, le cerveau et le sang, ainsi que réalisé des examens histologiques du côlon et des analyses bactériologiques. Chez les rats nourris avec un régime à base de blé et d'orge, les niveaux de MDA, ainsi que l'activité de la CAT et du GSH, étaient notablement plus élevés que chez les témoins. Par exemple, le cerveau présentait des niveaux de MDA plus élevés pour les groupes blé, orge et combinaison blé-orge (4,32±0,44 µmol/l), (4,37±0,76 µmol/l) et (4,29±0,28 µmol/l), respectivement, par rapport au groupe normal (2,47±0,89 µmol/l). De plus, les rats du groupe blé avaient un niveau de MDA plus élevé dans leur sang (3,73±1,37 µmol/l) par rapport au groupe normal.

En ce qui concerne le GSH, toutes les valeurs étaient élevées, même pour le groupe témoin. Par exemple, le groupe blé (2,37±0,38 µmol/mg) et le groupe orge (2,30±0,27 µmol/mg) avaient des valeurs rénales plus élevées que le groupe normal (2,27±0,21 µmol/mg). L'étude histologique a révélé que les rats traités avaient des colons plus épais avec une augmentation significative de l'épaisseur totale de la paroi du côlon chez les rats nourris avec du blé+orge (258,80µm) et de l'orge (192,77µm) par rapport au groupe normal (133,32µm), avec des différences de 125,48µm et 59,45µm, respectivement. De plus, des micro-organismes bénéfiques tels que Leuconostoc mesenteroides ont été découverts.

Ainsi, nos données montrent que les prébiotiques de blé et d'orge améliorent l'épaisseur du côlon, présentent des effets antioxydants et influencent positivement le microbiote intestinal et les paramètres de santé in vivo.

Mots clés : prébiotiques, blé, orge, activités biologiques, microbiote intestinal.

ملخص

تهدف هذه الدراسة إلى تقييم تأثير البريبايوتكس المستخلصة من القمح والشعير على ميكروبيوم الأمعاء ومعايير الصحة كبريبايوتكس وحصدا في (Hordeum vulgare) والشعير (Triticum aestivum) لدى الجرذان الويستار. تم اختيار القمح منطقة الوادي. تقيّم الدراسة التأثيرات البيولوجية في الجسم الحي لنظام غذائي غني بالقمح والشعير. تم تغذية الجرذان الويستار البيضاء الذكور بنظام غذائي يحتوي على 30% بريبايوتكس (قمح وشعير) و70% مابروما لمدة أسبوعين.

في الكبد، والكلى، (CAT) ، ونشاط الكاتالاز(GSH) ، والجلوتاثيون(MDA) قمنا بتقييم مستويات المالونديالدهيد والدماغ، والدم، بالإضافة إلى الفحوصات النسيجية للقولون والتحليل البكتيري. في الجرذان التي تم تغذيتها بنظام غذائي يحتوي على أعلى بشكل ملحوظ مقارنة بالمجموعة الضابطة. على سبيل المثال، GSHو CAT ونشاط MDA القمح والشعير، كانت مستويات في مجموعات القمح، والشعير، ومزيج القمح والشعير (0.44±4.32 ميكرومول/ل)، MDA أظهر الدماغ مستويات أعلى من (0.76±4.37 ميكرومول/ل)، و (0.28±4.29 ميكرومول/ل) على التوالي، مقارنة بالمجموعة العادية (0.89±2.47 في الدم (1.37±3.73 ميكرومول/ل) MDA ميكرومول/ل). بالإضافة إلى ذلك، كانت مجموعة القمح لديها مستوى أعلى من مقارنة بالمجموعة العادية.

فيما يخص الجلوتاثيون، كانت جميع القيم مرتفعة حتى بالنسبة للمجموعة الضابطة. على سبيل المثال، كانت مجموعة القمح (0.38±2.37 ميكرومول/ملجم) ومجموعة الشعير (0.27±2.30 ميكرومول/ملجم) لديها قيم أعلى في الكلى مقارنة بالمجموعة العادية (0.21±2.27 ميكرومول/ملجم). أظهرت الدراسة النسيجية أن الجرذان المعالجة لديها سماكة أكبر في القولون مع زيادة ملحوظة في السمك الإجمالي لجدار القولون لدى الجرذان التي تم تغذيتها بالقمح+الشعير (258.80 ميكرومتر) والشعير (192.77 ميكرومتر) مقارنة بالمجموعة العادية (133.32 ميكرومتر)، بفروق تبلغ 125.48 ميكرومتر و 59.45 ميكرومتر على التوالي. بالإضافة إلى ذلك، تم اكتشاف ميكروبات نافعة مثل Leuconostoc mesenteroides.

بذلك، تُظهر بياناتنا أن البريبايوتكس المستخلصة من القمح والشعير تحسن سماكة القولون، وتظهر تأثيرات مضادة للأكسدة، وتؤثر بشكل إيجابي على ميكروبيوم الأمعاء ومعايير الصحة في الجسم الحي...

الكلمات المفتاحية: بريبايوتكس، قمح، شعير، أنشطة بيولوجية، ميكروبيوم الأمعاء

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AX	**Arabinoxylan**
BHT	**B**utylated **H**ydroxy**t**oluene
CAT	**c**a**t**alase **a**ctivity
CAZymes	**C**arbohydrate-**a**ctive **e**nzymes
DHA	**d**ocosa**h**exaenoic **a**cid
DHA	**d**ocosa**h**exaenoic **a**cid
DP	**D**egree of **P**olymerization
DTNB	5,5'-**d**i**t**hio-bis-2-**n**itrobenzoic **a**cid
EPA	**e**icosa**p**entaenoic **a**cid
Fd	**d**ilution **f**actor
FOS	**F**ructo- **o**ligo**s**accharides
GC/MS	Chromatography-Mass Spectrometry
GIT	**G**astro**i**ntes**t**inal
GIT	Gastrointestinal tract
GOS	**g**alacto-**o**ligo**s**accharides
GPR	**G p**rotein-coupled **r**eceptors
GPX	peroxidase
GSH	**R**educed **g**lutathione
HCl	**H**ydrogen **c**hlor**i**de
HMOs	**h**uman **m**ilk **o**ligosaccharide**s**
HPLC	High-Performance Liquid Chromatography
ISAPP	**I**nternational **S**cientific **A**ssociation for **P**robiotics and **P**rebiotics
LA	**l**inoleic **a**cid
MDA	**m**alon**d**i**a**ldehyde
NMR	**N**uclear **M**agnetic **R**esonance
NS	**N**ormal **S**aline
PUFA	**p**oly**u**nsaturated **f**atty **a**cid
RS	**r**esistant **s**tarch
ROS	**R**eactive **o**xygen **s**pecies
SCFAs	**s**hort-**c**hain **f**atty **a**cids
SG	**S**ulfhydryl **g**roup
SOD	superoxide dismutase
TBA	**t**hiobar**b**ituric **a**cid
TCA	**T**richloroa**c**etic **a**cid

TOS	**T**rans galacto-**o**ligo**s**accharides
XOS	**x**ylo**o**ligo**s**accharides

SUMMARY

INTRODUCTION

Over the past decade, there has been a notable global shift in consumer purchasing habits, driven by an increasing awareness of wellness and the health benefits associated with dietary choices (Hansen, 2005; Yiridoe et al., 2005). This change reflects a broader understanding of the critical link between nutrition and overall well-being, influenced by evolving lifestyles and greater access to nutritional information (Divine & Lepisto, 2005; Quah & Tan, 2009). As a result, consumers are becoming more conscious of food safety and its direct impact on health, which has led to a heightened focus on the nutritional quality of food (Wang et al., 2018; Ghvanidze et al., 2017).

Among the various components of a healthy diet, non-digestible carbohydrates (CHO), collectively known as prebiotics, have garnered significant attention. Prebiotics encompass a variety of substances, including fibre, resistant starches, poly and oligosaccharides, and sugar polyols. These compounds play a vital role in supporting the growth and maintenance of gut microbiota, thereby enhancing metabolic activity, immune function, digestion, and nutrient absorption within the gastrointestinal tract (GIT) (Lockyer & Stanner, 2019). The shift towards recognizing the importance of prebiotics underscores a broader understanding of how specific dietary components can positively impact overall health, highlighting their essential role in the modern health-conscious paradigm (Mohr et al., 2020).

Prebiotics are remarkable in their ability to promote the growth of beneficial gut microbes. They can survive in acidic environments and resist digestion by enzymes in the small intestine, reaching the colon intact where they serve as a food source for gut bacteria. This fermentation process leads to the production of short-chain fatty acids (SCFAs), vitamins, and other beneficial metabolites, which contribute to gut health and overall physiological benefits (Yadav & Jha, 2019). Moreover, prebiotics can be sourced from various dietary ingredients such as chicory, chia seeds, dandelion greens, flaxseeds, onions, garlic, almonds, artichokes, oats, barley, and many other plants (Davani-Davari et al., 2019). These dietary sources enrich the gut microbiota, fostering an environment conducive to the growth and metabolic activity of beneficial microorganisms (Rolim, 2015).

In the context of this growing health-conscious trend, our study focuses on evaluating the impact of wheat and barley-derived prebiotics on gut microbiota and overall health in albino Wistar rats. Wheat (Triticum aestivum) and barley (Hordeum vulgare) were specifically chosen as prebiotics, and their biological effects were assessed in vivo. We aim to explore how these prebiotics influence the gut environment and contribute to overall health improvements. This research aligns with the increasing recognition of the importance of gut health in maintaining

overall wellness and provides valuable insights into the benefits of incorporating prebiotic-rich foods into the diet.

This work is structured into three chapters. The first chapter is devoted to a bibliographic synthesis that provides an overview of prebiotics. The second chapter focuses on biological tests linked to antioxidant activity, bacterial tests, and histological sections in vivo. The third chapter presents the main results obtained, followed by a discussion. A general conclusion and perspectives complete this work.

CHAPITRE I

Bibliographic synthesis

The subject of this chapter provides an overview of probiotics, including their definition, characteristics, types, natural sources, and their impact on intestinal microflora.

I.1.Definition of prebiotic

The word "prebiotics" has undergone substantial evolution in recent decades. The term "prebiotics" was first used in 1995 to refer to "non-digestible food components, which reveal beneficial effects on the host by selectively promoting the growth and multiplication of one or specific bacteria in the colon that significantly enhance the health of the host" (Gibson & Roberfroid, 1995). Prebiotics were also compounds at this period that might increase the number of bacteria, namely Bifidobacteria and Lactobacilli. The term "selectively fermented ingredients that particularly promote the activity and composition of gastrointestinal microflora and offer benefits to host health and well-being" was added to the definition in 2004, though, and now better describes the circumstances that have positive effects on the host. In light of this, prebiotics ought to be able to withstand host digestion and undergo fermentation in the intestinal microbiota (Gibson et al., 2004). The International Scientific Association for Probiotics and Prebiotics (ISAPP) revised the definition of dietary prebiotics to include “a selectively fermented ingredient that results in specific changes in the composition and activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health” in a unity report released in 2010, some years later. This was due to the advancement of molecular approaches and the accumulation of evidence regarding the density and diversity of bacterial communities (Gibson et al., 2010). The non-specific bacterial species are included in this amended definition, extending the range of bacterial species from the colon to the whole length of the gastrointestinal tract. Nonetheless, prebiotics have been defined as “non-digestible compounds that, through their metabolization by microorganisms in the gut, modulate the composition and/or activity of the gut microbiota, thus conferring a beneficial physiological effect on the host” by Bindels et al. (2015). This revised definition confined the prebiotic interaction with gut microbiota without engaging extra-intestinal habitats such as the respiratory system, vagina, and skin, but it also removed the basic conditions of selective fermentation processes and microorganism specificity (Bindels et al., 2015). In 2017, ISAPP revised the prebiotic concept once more, defining it as “a substrate, i.e., selectively used by host microorganisms and conferring a health benefit(s) to the host while retaining the microflora-mediated health benefits.” This was done in light of the most recent scientific and clinical advancements. With this revised definition, prebiotics are no longer restricted to GIT and carbohydrates; instead, they now include non-food components and extra-intestinal tissues. This revised definition is now also applicable to animals (Gibson et al., 2017).

When homeostasis is compromised, prebiotics are the compounds most frequently utilised to preserve a healthy gut microbiota and restore its balance (De Paulo Farias et al., 2019; Mohanty et al., 2018; Quigley, 2019). Prebiotics don't include any bacteria; instead, they are made up of materials that promote the growth of microorganisms (Olas, 2020). These nutrients are found in a variety of foods, such as raw oats, soybeans, and honey (Pokusaeva et al., 2011). On the other hand, plant oligosaccharides are the most widely used prebiotics (Pandey et al., 2015). Prebiotic properties are found in nondigestible carbohydrates such as polysaccharides (resistant starch, pectin, and dextrin) and oligosaccharides (fructooligosaccharides, galactooligosaccharide, Xylo oligosaccharides, isomalt oligosaccharides, mannooligosaccharides, raffinose oligosaccharides, arabinoxylan oligosaccharides, lactulose, and inulin) (Colantonio et al., 2020; De Paulo Farias et al., 2019; Mohanty et al., 2018).Prebiotics have the capacity to enhance human health by regulating the gut microbiome's equilibrium. The gut bacteria metabolize them, producing short-chain fatty acids such as acetate, butyrate, and propionate. Positive outcomes of short-chain fatty acid synthesis include enhanced intestinal membrane integrity and mineral absorption, reduced body weight and glucose levels, enhanced immunity, and altered metabolic, cardiovascular, and inflammatory indicators (De Paulo Farias et al., 2019). Additionally, consuming prebiotics encourages the development of good bacteria like Lactobacillus and Bifidobacterium, which restrict the growth of dangerous bacteria (De Paulo Farias et al., 2019; Mohanty et al., 2018).

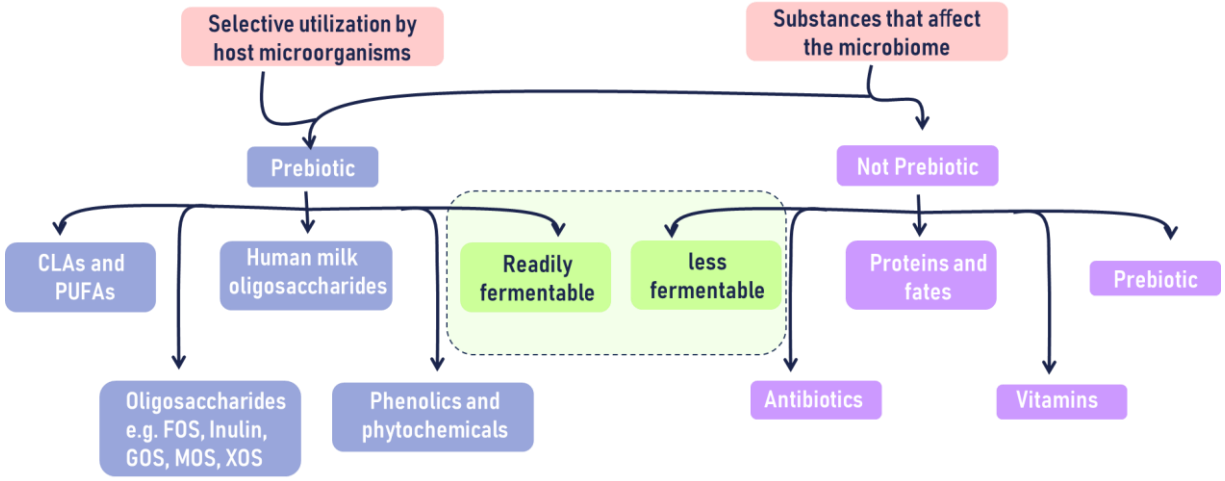


Figure 01. Using the suggested definition to differentiate between what is and is not a prebiotic (Gibson et al., 2017).

I.2.Characteristics of Prebiotics

Prebiotics are biomolecules containing 3 to 10 sugar moieties that are short, low molecular weight, and heat resistant. Because they have β-glycosidic linkages, they can withstand being hydrolysed by pancreatic and salivary enzymes from humans. Their low caloric value ranges from

4.l2 to 8.4 kJ g− 1. The structures of several common prebiotics are shown in (Figure 2). The following qualities make up the best prebiotics are:

- Neither mammalian tissues nor enzymes should be able to absorb them or hydrolyse them.
- They ought to selectively promote the development and proliferation of advantageous/probiotic bacteria.
- They ought to positively impact the gut microbiota's activities.
- The host defense system ought to benefit from them.
- They ought to be stable in the stomach and colon throughout a broad pH range.
- The host's defense mechanism ought to benefit from them (Panesar & Bali, 2016).

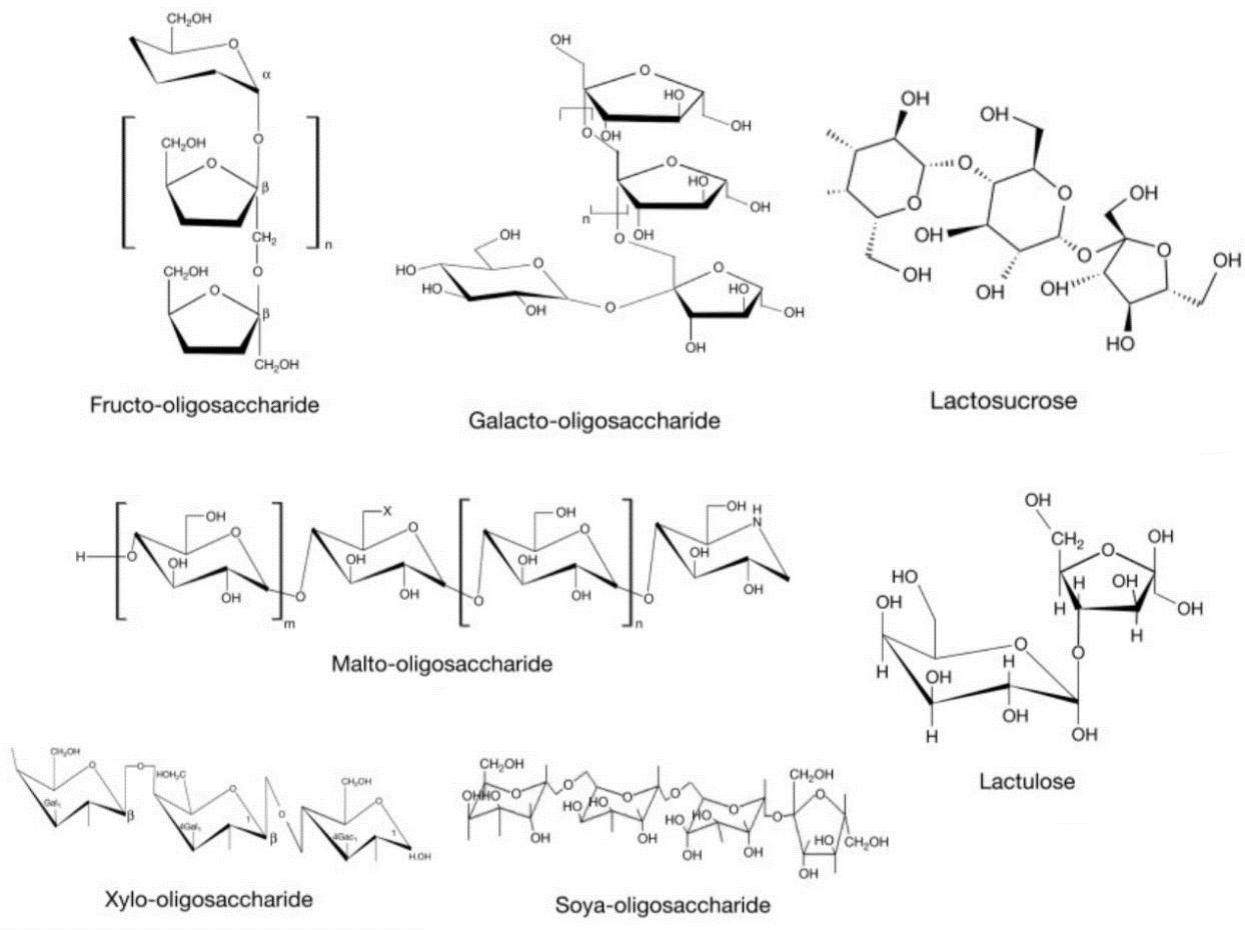


Figure 02. shows the structure of several common prebiotics (Panesar & Bali, 2016).

I.3.Types of Prebiotics

Prebiotics such as inulin, FOS, GOS, pyrodextrins, isomalto-oligosaccharides, lactosucrose, sugar alcohols, gluco-oligosaccharides, xylo-oligosaccharides, soya-oligosaccharides, lactulose, pectic oligosaccharides, Levans, and resistant starch are frequently used. Through transgalactosylation activity on respective carbohydrates, they may be generated chemically or enzymatically utilising a variety of substrates, including lactose, sucrose, starch, and Xylan (Figure 3). Prebiotics are produced by enzymes from many microbial sources, including bacteria, yeast, and fungi (Panesar & Bali, 2016).

Established prebiotics and emerging/tentative prebiotics are the two groups of prebiotics. Proven prebiotics consist of lactulose, GOS, FOS, and inulin. Isomalto-oligosaccharides, xylo-oligosaccharides, and soya-oligosaccharides are examples of emerging/tentative prebiotics. Additionally, prebiotics can be identified based on the substrate that was utilised to produce them, such as:

- prebiotics derived from lactose, such as GOS, lactosucrose, and lactulose;
- prebiotics derived from sucrose, such as FOS and isomaltose;
- prebiotics derived from starch, such as isomaltose-oligosaccharide and isomalt triose;
- prebiotics derived from Xylan, such as xylo-oligosaccharide (Panesar & Bali, 2016).

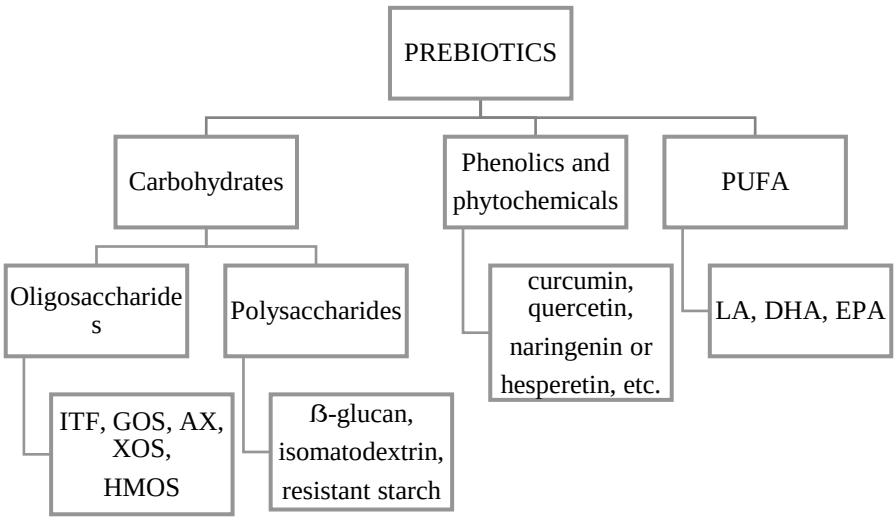


Figure 03. Prebiotic classification based on ISAPP. LA-linoleic acid; DHA-docosahexaenoic acid; EPA-eicosapentaenoic acid; GOS-galactooligosaccharide; AX-arabinoxylans; XOS-Xylo oligosaccharides; HMOs-human milk oligosaccharides; PUFA-polyunsaturated fatty acids (Kocot et al., 2022).

I.3.1. Fructans

Any carbohydrate in which the majority of osidic linkages are composed of one or more fructose-fructose links is referred to as fructan. Fructans are either β-2,1-linked inulin's or β-2,6-linked Levans, which are linear or branched fructose (oligo)polymers. A polydisperse carbohydrate molecule mostly, but not solely, composed of β-(2→1) fructosyl-fructose linkages is known as inulin. While numerous bacteria and certain fungi are the principal producers of Levans, it is mostly derived from plants (Reddy, 1999; Waterhouse & Chatterton., 1993).

Their terminal glucose units often feature β (2→1) linkage. FOS has a DP of less than 10, but inulin can have a DP of up to 60 (Louis et al., 2016).

Previous research suggested that fructans might specifically promote lactic acid bacteria. Nonetheless, recent studies have demonstrated that a crucial factor in identifying the bacteria capable of fermenting fructans is their chain length (Scott et al., 2014). As a result, fructans can also directly or indirectly support other bacterial species.

I.3.2. Galacto-Oligosaccharides

Lactose extension products, known as galacto-oligosaccharides (GOS), are divided into two subgroups: (i) GOS containing extra galactose at C3, C4, or C6, and (ii) GOS produced by enzymatic trans-glycosylation of lactose. A combination of tri-to Penta saccharides with galactose in β (1→6), β (1→3), and β (1→4) links is the predominant end product of this process. Trans-galacto-oligosaccharides, or TOS, is another name for this kind of GOS (Gibson et al., 2010; Macfarlane et al., 2007).

GOSs can considerably boost Bifidobacteria and Lactobacilli. Babies' bifidobacteria have a high integration rate with GOS. Though not as much as Bifidobacteria, Enterobacteria, Bacteroidetes, and Firmicutes are activated by GOS (Louis et al., 2016).

Some GOSs are made from the lactose isomer lactulose. These GOSs generated from lactulose are also regarded as prebiotics (Gibson et al., 2010).

I.3.3. resistant starch

RS is the portion of starch that passes through the small intestine undigested and into the big intestine. Hence, in the gastrointestinal system, RS is the portion of starch that functions similarly to dietary fibre. Recent research has connected the small intestine's resistance to enzymatic digestion (Englyst et al., 1992) to a host of advantageous physiological effects on health, including an improvement in cholesterol metabolism, a prebiotic effect on colon

microflora, and a decreased risk of colon cancer and ulcerative colitis (Shi et al., 2013; Ozturk et al., 2009).

The small intestine breaks down starch, which is essentially glucose molecules joined by a-D-(1→4) or a-D-(1→6) glycosidic bonds. It is mostly made up of two components: amylopectin, which is highly branched and has both a-D-(1→4) and a-D-(1→6) connections, and amylose, which is made up of straight chains that make up 15-20% of starch and have a-D- [1→4] linkages (Panesar & Bali, 2016).

The highly branching shape of amylopectin increases the surface area in the small intestine that is available for digestion. Because resistant starch has more amylose, its exposed surface area is less. As a result, starches high in amylose breakdown more slowly and some of them pass through the small intestine and into the colon (Panesar & Bali, 2016).

Four classifications are further distinguished for resistant starch based on its complexity and structure.

Table 01. Classification of resistant starches (Champ, 2004).

Type	Principal feature	Illustrations of RS or RS sources
RS 1	Physically inaccessible starch	Grain legumes (beans, lentils)
RS 2	Resistant starch granules	Unripe banana, raw potatoes
RS 3	Retrograded starch	Cooked and cooled potatoes, stale bread
RS 4	Chemically modified starch	Cross-bonded starches

I.3.4. Polyphenols

Multiple phenol units define the broad class of secondary metabolites known as polyphenols. These bioactive substances, which are abundant in a wide range of fruits, vegetables, and crops, are potent antioxidants that may lower the risk of noncommunicable illnesses (Koch, 2019). Since bacteria metabolises polyphenols in the gut and their derivatives have health advantages, polyphenols also fall under the new concept of prebiotics. Although there has been a substantial rise in research on polyphenols in recent decades, this is a very large class of substances where there can be significant variation in activity between classes. Even though in vivo animal models were used in more research, several clinical trials were carried out and a few more were registered on clinicaltrail.gov (Bernardi et al., 2019).

The kind of bioactive substances used, the length and dosage of the sickness, the kind of animals or subject population, and other factors vary between these investigations. Interactions between polyphenols and gut bacteria are presented in a recent review by Plamada and Vodnar (Plamada & Vodnar, 2021). In a very good review, the impact of polyphenols on gut barrier functions was summed up (Koch, 2019).

I.3.5. Polyunsaturated Fatty Acids

Polyunsaturated fatty acids are another recent addition to the prebiotic family (PUFA). Even while PUFA were listed as potential prebiotics in the ISAPP definition (Hill et al., 2014), there is currently insufficient proof in the form of comprehensive research to support this claim (Rinninella & Costantini, 2022). Notably, not all PUFA may be regarded as prebiotics according to current knowledge. Potential prebiotic options were omega-3 fatty acids (eicosapentaenoic acid, or EPA; C20:5), omega-6 fatty acids (linoleic acid, or LA; C18:2), and docosahexaenoic acid, or DHA; C22:6) (Rinninella & Costantini, 2022). Since Durkin et al.'s recent study provided an overview of the impact of omega-3 fatty acids on the intestinal barrier (Durkin et al., 2021).

I.4.Natural Prebiotic Sources

Different plants naturally contain a variety of indigestible carbohydrates (Prado et al., 2019). (Figure 4) depicts the methodical arrangement of several natural prebiotics and the advantages that go along with them.

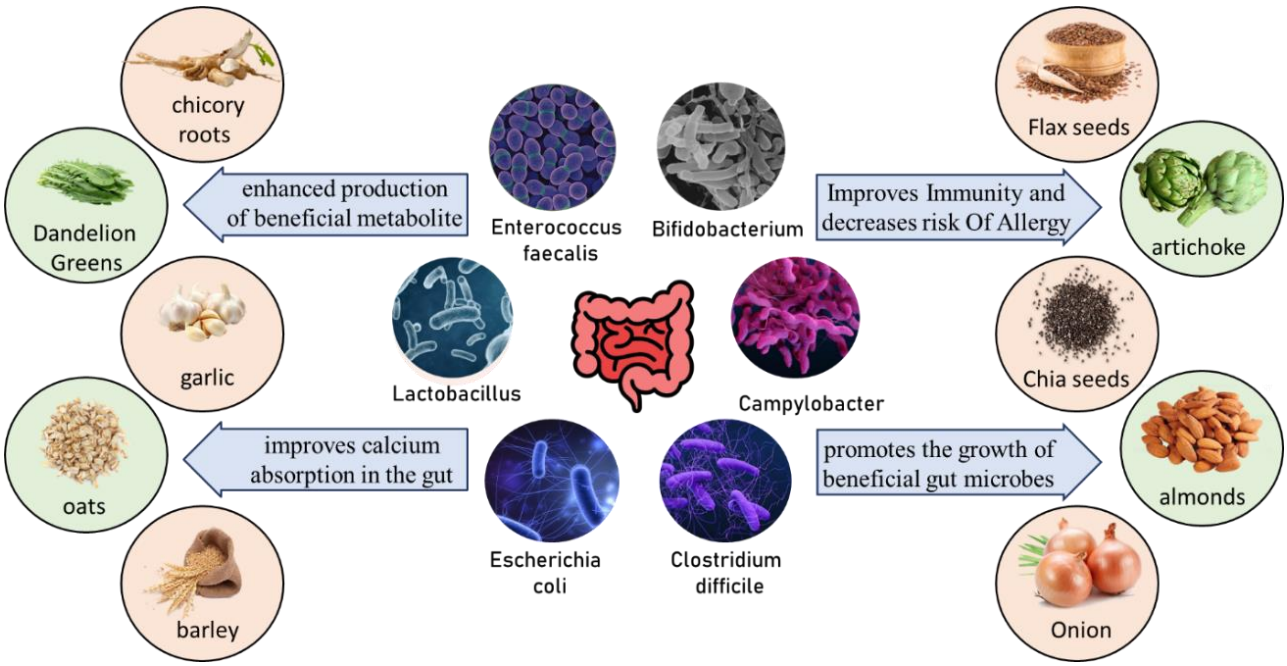


Figure 04.A diagrammatic representation of prebiotic sources and functions (Kaur et al., 2021).

Table 02. Types, Sources, Impact on gut bacteria, and potential benefits of prebiotics.

Type of prebiotic	Sources of prebiotic	Impact on gut bacteria	beneficial effect	References
Fructans	asparagus, garlic, leek, onion; artichoke, endive or witloof, Jerusalem artichoke. Etc.	Bifidobacteria and Lactobacilli species	improve the level of glucose, modulate lipid metabolism reduce plasma membrane LPS as well as diacylglycerides.	Fuchs (1991) (Ortega-González et al., 2014)
GOS	Human's milk and cow's milk, soybean, lentil, and chickpeas. Etc.	Increasing bifidobacteria and lactobacilli	selective growth of good bacteria, particularly lactobacilli and bifidobacteria, in the gut that reduces endogenous and exogenous intestinal infections by providing resistance against pathogen colonisation.	Alander et al. (2001) (Saavedra, 2023) (Muzaffar et al., 2021) (Sangwan et al., 2011)
RS	Nonwaxy rice grains, wheat, Barley, maize...etc.	Increasing Bifidobacteria and Lactobacilli	laxation, hypocholesterolemia and hypoglycemic effects and reducing the risks of ulcerative colitis and colon cancer	(Kim et al., 2006; Shu et al., 2006) (Butardo & Sreenivasulu, 2016) (Tacer-Caba & Nilufer-Erdil, 2019)
Polyphenol	grape, olive, blueberry, penile leaf, cowpea, caraway, sweet potato leaf, soy bean (green), pepper leaf, ginseng leaf, chives, and broccoli…etc.	Increasing Bifidobacteriaceae and Lactobacillaceae Reducing Escherichia coli, Clostridium perfringens, and Helicobacter pylori	reduced risk of cardiovascular disease, reduced oxidative stress in serum, anticancer	(Li et al., 2014) (Dias et al., 2021) (Gowd et al., 2019)
PUFA	soybean oil, corn oil, cottonseed oil, nuts..etc.	Increasing Bifidobacteria and Enterobacteria	improved insulin resistance and decreased pro-inflammatory state	(Perona, 2017) (Adefegha et al., 2022) (Cani et al., 2007) (Lam et al., 2012)

I.5.The effects of prebiotics on intestinal microflora

Trillions of bacteria, fungi, archaea, and protozoa inhabit the human gastrointestinal tract, and these microorganisms are essential to many biological processes, including immune system development, host tolerance to pathogens, and nutrition breakdown (Belkaid and Hand, 2014, Brestoff and Artis, 2013). The use of nondigestible substrates to change the makeup or metabolic activity of resident bacteria is one of the key strategies in the microbiota-mediated approaches to human health improvement that were first proposed more than a century ago (Metchnikoff, 1907) (Roberfroid et al., 2010). These nondigestible substrates, subsequently designated as prebiotics, include (but are not limited to) inulin, FOS, GOS, lactulose, and galactose. They operate as a medium for saccharolytic bacteria.

Prebiotic supplementation has been shown to alter the quantity and makeup of certain gut bacteria in both human clinical trials and animal models. In one study, prebiotic-treated mice's faecal microbiota showed significant increases in genera like Akkermansia, Dehalobacterium, Prevotella, Sutterella, and Tannerella, while other genera (Alistipes, Allobaculum, Clostridium, Coprobacillus, Coprococcus, Eubacterium, Faecalibacterium, and Ruminococcus) showed drastic decreases (Everard et al., 2014). According to Everard et al. (2014), the genera Scardovia and Propionibacterium were only found in prebiotic-treated (control and high-fat diet) mice, whereas Akkermansia, Bifidobacterium, and Sutterella were not detectable under high-fat diet treatment alone but were after receiving prebiotic treatment in high-fat diet mice.

Every study found a rise in Bifidobacterium at the genus level, and the majority of them also found an increase in Lactobacillus. Overall, research showed that prebiotics have the ability to raise the number of beneficial and decrease the number of harmful members of the gut microbiota, improving the host colonic microbiota and moving it in the direction of a healthier composition. These binary situations are troublesome, though, as there is disagreement about which gut microbiota microbes are advantageous and harmful, and it's not even clear if such a categorization is even feasible (Bindels et al., 2015). These restrictions point to a more thorough connection between prebiotics and the gut microbiome. Thus, the only way to elucidate the mechanisms of prebiotic activity and ascertain their actual involvement in fostering gut health is to track changes in the overall population.

I.6. Polysaccharides

Based on the number of sugar units they contain, carbohydrates are classified into the following categories: (a) monosaccharides, which have one sugar unit; (b) disaccharides, which

have two sugar units; (c) oligosaccharides, which have three to ten sugar units and can be created by dissolving polysaccharides; and (d) polysaccharides, which are macromolecules made up of more than ten monosaccharides (Aranceta-Bartrina & Serra-Majem, 2001). Dietary fibre mostly consists of polysaccharides (Lovegrove et al., 2015). In the small intestine, they attach to bile acids, which lowers serum cholesterol and returns blood lipid levels to normal (W. Huang et al., 2022). The majority of polysaccharide structures are often found in more complex structures that also contain digestible proteins and carbs, and they are linked to a number of biological advantages for gut health (Meyers et al., 2006).

Prebiotics are indigestible but fermentable polysaccharides that have the ability to increase the number and activity of good bacteria in the colon. Thus, among other advantages, the host metabolism, fat storage, and insulin resistance are all improved by include polysaccharides in the diet (Ahmadi et al., 2017). Bacterial polysaccharides, which are often present in the cell wall, also have immunomodulatory properties. Host-derived polysaccharides influence intestinal health in general and shield host cells from harmful microbial neighbours by interacting with gut microorganisms (Ho et al., 2020).

I.7. Intestinal Microbiota

The intestinal microbiota serves as a dynamic organ crucial for maintaining overall health. The gut's complex community of tiny creatures, known as the intestinal microbiota, is home to around 100 trillion bacteria, viruses, protozoa, and fungus (Gilbert et al., 2016). From the stomach to the colon, these bacteria become more diverse and denser (Hornung et al., 2018). They engage in crucial physiological processes for the host and build intricate connections with one another that can be mutualistic or competitive, all of which have an impact on the host's health in one way or another (Partida-Rodríguez et al., 2017). The majority of human physiological processes, including metabolic and pathogenic processes as well as the development of the immune system, are influenced by the gut microbiota, either directly or indirectly (Shreiner et al., 2015). Together with being integrated into macro-ecosystems, such as eukaryotic hosts, and being essential to their health and functioning, the microbiome also includes all of the genetic information found in the microbiota (Plaza-Díaz et al., 2021), resulting in a dynamic, interactive micro-ecosystem that is capable of changing over time and on a large scale (Berg et al., 2020).

Since functionally related microorganisms within an intact ecosystem may be able to balance the function of other species that have gone extinct, a gut ecosystem with a broad range of species may be more robust to external impacts than one that lacks diversity. As a result, increased variety is frequently thought to be a sign of a digestive tract in good condition (Sommer,

Rühlemann, et al., 2017; Sommer et al., 2017). Therefore, great taxonomic diversity, a stable core microbiota, and high microbial gene richness are often seen in an equilibrated microbiota community. The gut microbiota interacts symbiotically with the host and is robust and stable under healthy circumstances (Hou et al., 2022; Fan & Pedersen, 2020). On the other hand, dysbiosis, or an imbalance in the composition and function of the gut microbiota, has been connected to a number of conditions, including brain disorders (Jiang et al., 2015), liver disease (Ling et al., 2015), cancer (Fernández et al., 2018; Michaud et al., 2012), respiratory diseases (Honda & Littman, 2016; Huang et al., 2011), diabetes (De Groot et al., 2017), inflammatory bowel disease (Kleessen et al., 2002), and cardiovascular disease (Sánchez-Rodríguez et al., 2020), chronic kidney disease (Vaziri et al., 2013).

Numerous research on the topic of omics have demonstrated the importance of the communication between microbes and hosts in the functioning of the gut microbiota. One of the main genera of intestine resident bacteria that make up the mammal colon flora is Bifidobacteria. Bifidobacteria uses a variety of tactics in highly competitive environments, such as glycan-harvesting, glycan breakdown, and cross-feeding, to survive in the intestinal environment of mammals. This leads to alterations in the microbiota's composition and in the metabolism of microorganisms, such as a change in the rate at which short-chain fatty acids are produced and the utility of carbohydrates (Turroni et al., 2016). For instance, Bifidobacteria longum metabolises arabinoxylan oligosaccharides into acetate, which Eubacterium rectal can then convert into butyrate. Eubacterium rectal also produces xylose, which promotes the synthesis of acetate (Rivière et al., 2015). There are predatory connections among microorganisms as well. For instance, Bdellovibrio bacteriovorus feeds on other bacteria, which helps maintain the balance and quantity of bacteria in bacterial communities (Dwidar & Yokobayashi, 2017; Atterbury et al., 2011). Bacterial overgrowth or undergrowth can be caused by an imbalance in the gut microbes, which leaves the environment open to harmful bacterial invasion (Lozupone et al., 2012). The simultaneous synthesis of toxins by pathogenic bacteria affects the microbiota (Stein et al., 2013) and may result in host disorders (Voth & Ballard, 2005).

Nutritional, chemical, and immunological gradients along the gut affect the density and composition of the microbiota (Thursby & Juge, 2017). In comparison to the small intestine, the large intestine has a longer transit time and higher concentrations of oxygen, acids, and antimicrobials (Donaldson et al., 2015). But fast-growing bacteria and facultative anaerobes that may stick to mucous or epithelial surfaces are assumed to survive in the large intestine (Donaldson et al., 2015). The colon is home to a rich and varied colony of bacteria, mostly anaerobes that can

use complex carbohydrates that the small intestine cannot break down. Prevotelaceae, Lachnospiraceae, and Rikenellaceae are said to make up the bulk of the species in the colon (Thursby & Juge, 2017; Boscaini et al., 2022).

I.8. Metabolism of Dietary Polysaccharides by Gut Microbiota

Following ingestion, food travels through several intricate digestive processes inside the human body before becoming tiny nutrient molecules that the body may absorb and use (C. Li et al., 2020). Among these, the starch in rice and other meals high in polysaccharides can be broken down and absorbed by the body to produce energy, whereas other foods, such as the fibre in vegetables, cannot (Cheng & Hu, 2022; Hernández-Maldonado et al., 2019). These complex polysaccharides cannot be further broken down by the body because it lacks the necessary enzymes. However, the intestinal flora may make use of them and encourage the creation of related metabolites, which in turn improve human health (Ding et al., 2019; Martens et al., 2011).

These food polysaccharides fall into two categories—fermentable and non-fermentable—depending on whether the body can break them down and absorb them. The intestinal flora will use and break down the fermentable polysaccharides, whereas the non-fermentable ones will ultimately be eliminated with faeces (Ahmadi et al., 2017).

The mystery is the existence of enzymes in intestinal microorganisms that can break down dietary polysaccharides, like Firmicutes and Bacteroides, which account for a significant portion of the human intestinal flora (Kaoutari et al., 2013). Several microorganisms have been identified to date that can use dietary polysaccharides. Research has demonstrated that intestinal flora is capable of producing carbohydrate-active enzymes (CAZymes). Subsequent investigations have revealed that CAZymes may break down complex polysaccharides into fermentable monosaccharides, hence significantly facilitating the body's utilisation and absorption of polysaccharides (Wardman et al., 2022; Aakko et al., 2020). Because the body is unable to digest and use these dietary polysaccharides, the intestinal flora uses them as a source of energy. By fermenting these polysaccharides, the flora is able to produce more metabolites, including SCFAs, for its own energy needs (Yao et al., 2020). Common SCFAs include propionic acid, acetic acid, and butyric acid. SCFAs are representative of a broad spectrum of products of the intestinal flora, and they consist of a carboxylic acid and a tiny hydrocarbon chain (carbon chain length of six carbon atoms or less) (Bolognini et al., 2015). Bacteria create metabolites called short-chain fatty acids (SCFAs), which can interact with host cells and cross the intestinal barrier to influence the immune response (Martin-Gallausiaux et al., 2020). SCFAs are produced by the metabolism of proteins and polysaccharides by gut bacteria during the anaerobic fermentation of fibre (Aranceta-

Bartrina & Serra-Majem, 2001). We provide a summary of the fermentation-induced bacterial breakdown of polysaccharides in the colon in Figure 5.

An increasing amount of research indicates that SCFAs can control immune cells' inflammatory responses, such as those of neutrophils, dendritic cells, macrophages, monocytes, and T cells (H. Zhang et al., 2022; Sanchez et al., 2020; Yao et al., 2020).

Nondigestible carbohydrates are hydrolysed by obligatory anaerobes into oligosaccharides, which are then fermented in an anaerobic setting. Anaerobes use a mechanism akin to glycolysis to convert hexoses to pyruvate, which is then oxidised to acetyl-CoA along with the reduction of an electron carrier or, frequently, hydrogen gas (Rowland et al., 2017; Kaoutari et al., 2013). Acetyl CoA is then changed into a variety of SCFAs.

Colocytes immediately absorb SCFAs upon their production, mostly via H+- or sodium-dependent monocarboxylate transporters. By binding to G protein-coupled receptors such as GPR109a/HCAR2 and GPR164, as well as free fatty acid receptors 2 and 3, SCFAs impact intestinal mucosal immunology and barrier integrity and function (Silva et al., 2020; Besten et al., 2013).

When SCFAs bound to GPR43 and GPR109A in a mouse model of colitis brought on by dextran sulphate sodium, this enhanced K+ efflux and hyperpolarization led to the activation of the NLRP3 inflammasome and elevated blood levels of IL-18 (Macia et al., 2015). Because of this, SCFAs and their receptors support the health advantages of dietary fibre and the process by which metabolite signals filter through to a key pathway for gut homeostasis. The maintenance of intestinal immunological homeostasis is significantly aided by SCFAs (J. Cheng et al., 2022; Desalegn & Pabst, 2019; F. Chen et al., 2018). Pathogens might be stopped from invading by immune responses induced by ratifying and eliminating antigens from neutrophils and monocytes (J. Cheng et al., 2022; Desalegn & Pabst, 2019; F. Chen et al., 2018).

The host's gut epithelium uses the 50–100 mmol·L−1 SCFAs produced daily by the typical gut microbiota as an energy source (Duncan et al., 2009). These SCFAs have a wide range of functions in controlling gastrointestinal motility, inflammation, energy absorption, and glucose homeostasis. They may be quickly absorbed in the colon (Cani et al., 2013; Flint et al., 2012).

The most prevalent SCFAs are propionates, butyrate’s, and acetates. Acetates are oxidised in muscle and undergo lipogenesis in adipose tissue, and bacteria may also convert certain acetates into butyrate’s (Hou et al., 2022). Propionate and butyrate both shield the body from the damaging

effects of hypertension on the heart (Bartolomaeus et al., 2019), and butyrate's are also linked to the integrity of the intestinal barrier and may benefit the gut's epithelium (Mathewson et al., 2016).

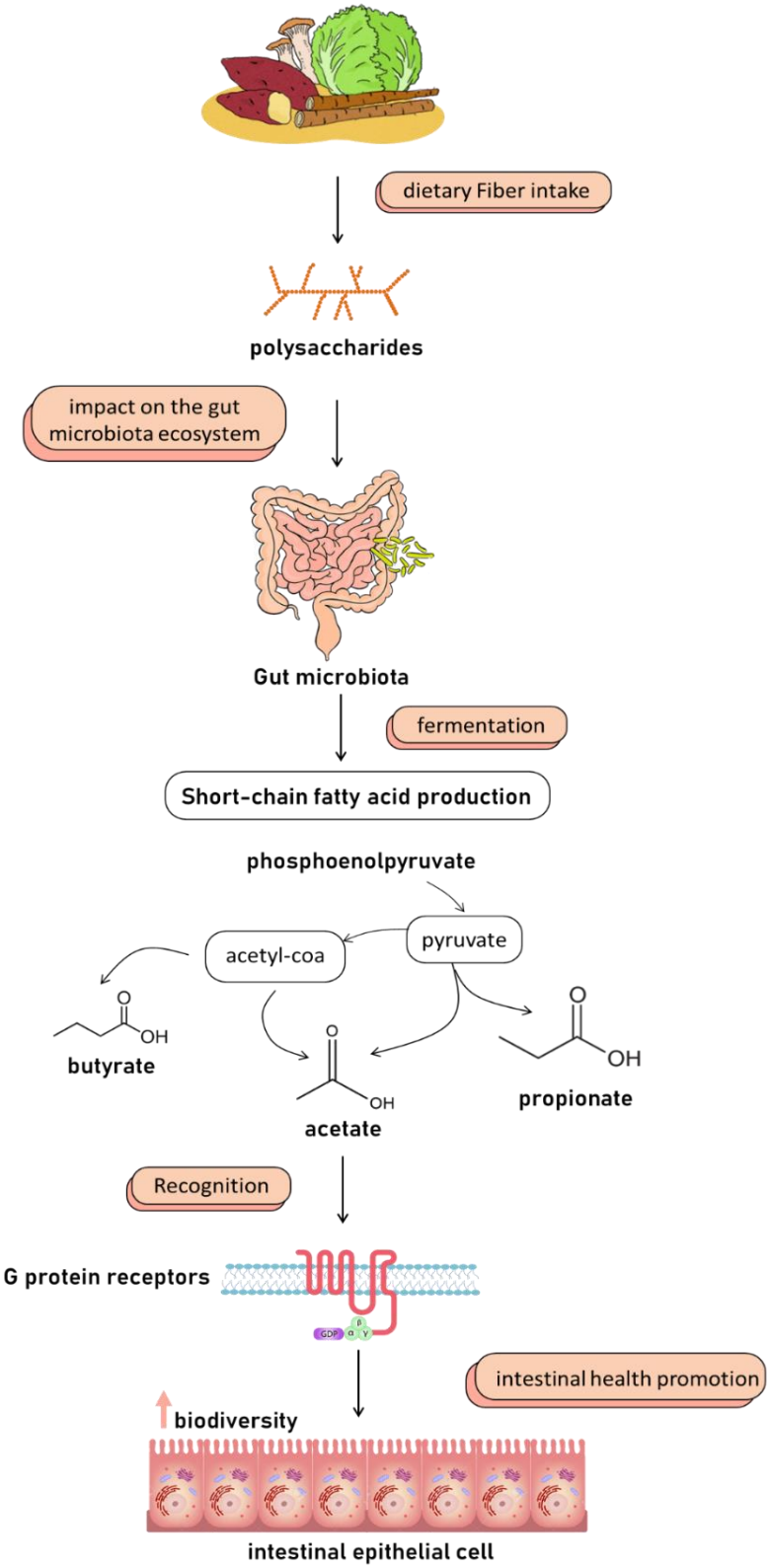


Figure 05. illustrates the way polysaccharides are broken down by bacteria in the colon during fermentation (Álvarez-Mercado & Plaza-Díaz, 2022).

CHPITRE II

Material and methods

The work methodology concerns the principle of the study, effect of Wheat (Triticum aestivum) and barley (Hordeum vulgare) (prebiotic) on gut microbiota and general health and a set of biological tests linked to antioxidant activity and Bacterial test, Histological sections.

II.1. Study Concept

More than a thousand different types of microorganisms, totalling over 1014 microorganisms—nearly ten times the number of somatic cells—are found in the gastrointestinal tracts of humans and other animals (Yatsunenko et al., 2012; Qin et al., 2010). The majority of gut microorganisms are bacteria, and these and their metabolites function as a link between the host and its diet in addition to playing significant roles in biological processes like nutrition utilisation, host resistance against infections, immune system maturation, and host metabolism (Belkaid and Hand, 2014, Brestoff and Artis, 2013). More than a century ago, Metchnikoff. (1907) originally postulated that altering the human microbiome may benefit health. These days, this idea includes a wide range of treatment approaches, from introducing individual microbes or consortia of these organisms (probiotics) to transplanting the complete faecal microbiota (Olle, 2013). Providing growth substrates for resident microbes to produce compositional or metabolic changes is another crucial strategy that integrates the idea of prebiotics (Roberfroid et al., 2010). Prebiotics have been used extensively for many years by both people with intestinal disorders and the general public, and they have a very good safety record (Doron and Snydman, 2015; Didari et al., 2014).

The aim of this study is to evaluate the impact of wheat and barley-derived prebiotics on gut microbiota and overall health in albino Wistar rats. Wheat (Triticum aestivum) and barley (Hordeum vulgare) were specifically chosen as prebiotics, and their biological effects were assessed in vivo.

II.2. Study material

Both biological and non-biological materials, such as the tools and substances utilised in the experiment, are represented in the research material. The selected animal model and plant species make up the biological material.

II.2.1. Plant material

The plant material consists of untreated wheat and barley from the Wilaya of El-Oued, in Southeastern Algeria. It is harvested in May and June of 2023 and is provided to us by the Dry grains and legumes cooperative (ccls) in El Oued.

The portions of the plant chosen for this activity are the cereals of wheat and barley after harvest. Until the dry mass is stabilised, drying is done for two weeks at room temperature (20 to

25°C) in a dry, shady area. Then, using a MILL, cereals are pounded into a powder. This powder is then properly kept in a cold, dry location so that it may be used when the experiment begins.

II.2.2. Animal material

Male Wistar rats, weighing between 120 and 200 g, are utilised in an in vivo study to evaluate the biological activities of prebiotics. They were acquired from the Faculty of Natural and Life Sciences at Echahid Hamma Lakhder University (Algeria, El-Oued). The rat was selected as the model of choice because it is a good fit and has been extensively used to investigate the in vivo fermentation of non-starch polysaccharides NSPs (such pectin and β-glucan) and how that affects the control of eating behaviour (Knudsen, 2011; Adam et al., 2014). Throughout their adaptation phase, the animals were kept in cages in an animal facility at the Faculty of Natural and Life Sciences, Echahid Hamma Lakhder University, in isolation for two weeks. The light/dark cycle was 12 h/12 h, and the temperature was 21 °C (Tian et al., 2019). Following acclimation, the animals were split into four experimental groups, each consisting of eight rats, at random. Food and water were fed *ad libitum*. For two weeks, the animals in each group were fed a specific diet for two weeks.

II.3. Study methods

The study's techniques imply a prebiotic-rich diet and the assessment of biological activity in vivo.

II.3.1. diet preparation

To construct the diet, we combined 30% prebiotic (wheat and barley) with 70% mabroma (soy, corn, bran, limestone phosphates, C.M.V oil acid compounds) (Tian et al., 2019). After gathering the materials beside the water, we produced something known as safa. We prepare the food in the same manner as our traditional dish safa (Photo 01). Each diet was formulated based on a total daily intake of 200g, with 30% being prebiotic and 70% mabroma. We've divided the diet into four sections: 30% of the diet is made up of wheat and 70% is made up of mabroma; 30% of the diet is made up of barley and 70% is made up of mabroma; the third section of the diet is made of 30% divided into 15% wheat, 15% barley, and 70% mabroma; and the fourth segment is made up entirely of mabroma (Figure 6) for two weeks (Rodriguez et al., 2023; Dongowski et al., 2003; Dongowski et al., 2002; Adam et al., 2002; Adam et al., 2001).

Photo 01. diet preparation as safa (original photo).

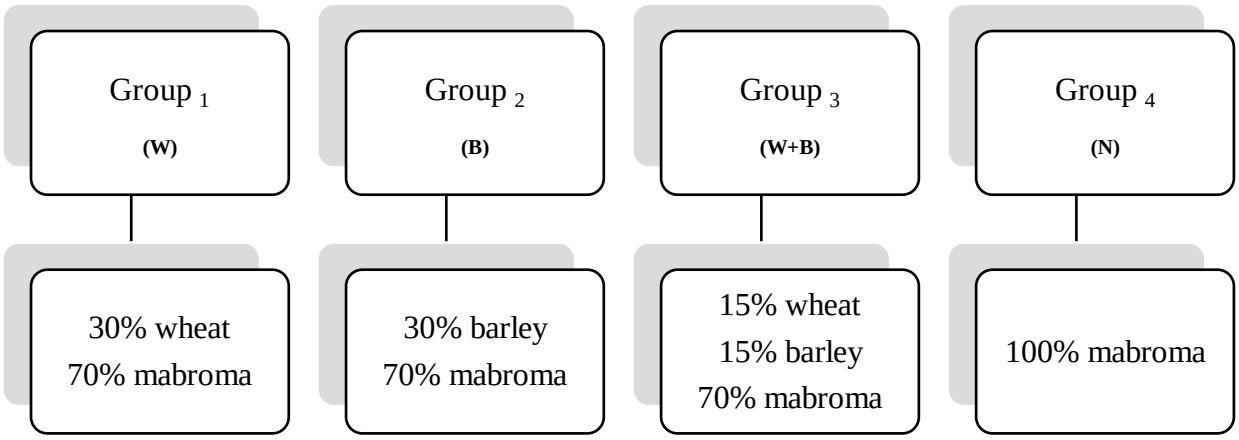


Figure 06. An illustration illustrating how each experimental group's diet was divided down.

II.3.2. Sacrifice and collection of blood and organs

The rats were starved for sixteen hours, anesthetized with chloroform (94%), decapitated, and their blood was collected in heparin tubes to finish the experiment (KAMALI and MOHRI, 2015; MOHRI and REZAPOOR, 2009). Centrifugation at 3000 rpm takes 15 minutes to separate the serum, which is then kept cold for subsequent use (Woo et al., 2013). The liver, brain, and kidney are dissected, and then they are cleaned with sodium chloride. Organs are kept for use in homogenate preparation. This allows us to examine the components of oxidative activity, such as the concentration of malondialdehyde (MDA) and the catalase activity (CAT), Reduced glutathione (GSH). The intestines are promptly preserved in a 10% formalin solution for histological analysis (figure 8).

For the microbial test, we take a biopsy swab from two rats in each group next to Bec Bunsen for sterile conditions and place it in a container filled with 2.5 ml of Normal Saline (NS). The swab containers are then stored at 4°C for future use (figure 7).

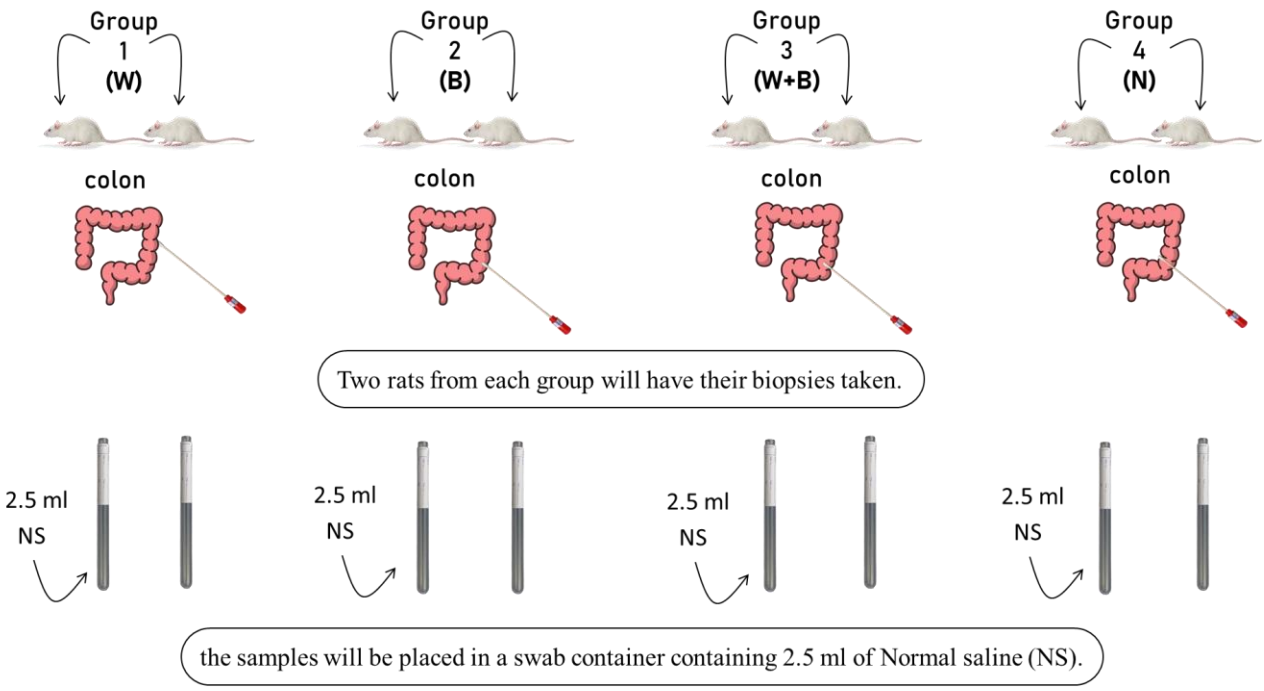


Figure 07. An illustration showing steps to conduct the microbiological test (original figure).

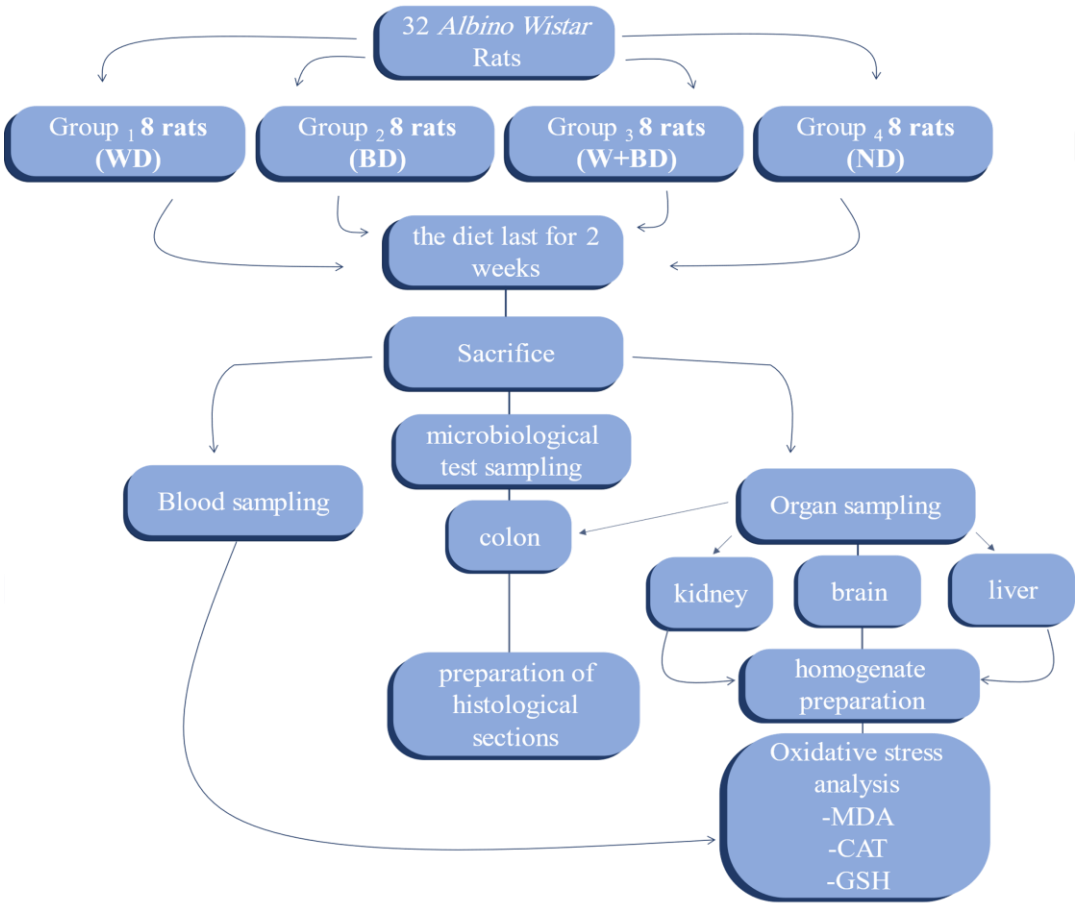


Figure 08. Synopsis of the in vivo study's experimental methodology.

II.3.3. Oxidative stress parameters

The dosage for measuring malondialdehyde (MDA) levels and catalase activity (CAT), as well as reduced glutathione (GSH), has been selected.

II.3.3.1. homogenate Preparation

To create a tissue solution, one gramme of each of the three rat tissues (brain, kidney, and liver) is weighed, crushed, and homogenised in TBS (50 mM Tris, 150 mM NaCl, pH 7.4). For twenty minutes, the mixture is centrifuged at 3900 rpm. For subsequent usage, the produced supernatant is kept at − 4 °C (BOUSSEKINE et al., 2014).

II.3.3.2. Malondialdehyde (MDA) assay

II.3.3.2.1. Principle

This test's basic idea is based on the condensation of MDA molecules in an acidic (pH 2–3) solution. When heated with thiobarbituric acid (TBA), this process generates a pink colour due to the formation of an MDA compound bound with two molecules of thiobarbituric acid. The absorbance is measured using a spectrophotometer at 532 nm (DEROUICHE et al., 2019; DEROUICHE et al., 2017; SASTRE et al., 2000; YAGI, 1976; OHKAWA et al., 1979).

II.3.3.2.2. MDA Solution

A solution is made in a beaker using 375 mg of TBA, 20 g of TCA, 0.01 g of BHT, 25 ml of HCL (1 N), and 50 ml of distilled water. In a water bath, the solution is heated at 40°C until the TBA is entirely dissolved. The combination is then moved to a 100 ml flask, and distilled water is used to adjust the volume to the desired level (LAIB, 2023).

II.3.3.2.3. Mode of operation

Add 1 ml of TBA reagent and 200 µl of sample to glass and screw test tubes. After sealing the tubes hermetically, the mixture is heated for fifteen minutes at 100°C in a Marie bath. The tubes are left open during cooling in a cold-water bath for thirty minutes to allow the gases produced during the reaction to escape. Using a spectrophotometer, the absorbance of the supernatant is measured at 532 nm following five minutes of centrifugation at 3000 rpm (LAIB, 2023).

II.3.3.2.4. Presentation of the findings

MDA (µmol/mg of tissue) = (Do sample/1.53 x 105)/mg of tissue

II.3.3.3. Catalase enzymatic activity (CAT) assay

II.3.3.3.1. Principle

Catalase is a powerful antioxidant enzyme found in many tissues, such as the liver, mitochondria, and red blood cells. It consists of four protein subunits (KIRKMAN et al., 1999; SCHEIBMEIR et al., 2005; REES et al., 2007; VAMECQ et al., 2004). Catalase limits the formation of hydroxyl radicals from hydrogen peroxide (ZOUAGHI, 2011). The excess H2O2 can form complexation with ammonium molybdate to produce a light-yellow solution (Zhang et al., 2017). Catalase activity is expressed by measuring the catalase-induced disappearance of H2O2 present in the sample, by measuring the absorbance of H2O and O2 produced by the reaction at 560 nm (COULIBALY et al., 2022).

II.3.3.3.2. Mode of operation

One millilitre of pH 7.2 phosphate buffer (0.1 M, 0.1 M Hg), 0.975 millilitres of prepared H2O2 (0.091 M), and 0.025 millilitres of enzyme source (sample) are mixed together in a test tube. For four minutes, the absorption value at 560 nm is instantly recorded once per minute.

$$\text{catalase activity (µmol/H2O2/min/mg)} = \frac{(\Delta DO)}{\varepsilon \times L \times \text{[illegible]}} Fd \times 100$$

II.3.3.3.3. Presentation of the findings

ε: Extinction coefficient (= 0.043 mM-1.cm-1).

L: The length of the cuvettes used (1 cm).

Fd: 0.02 (dilution factor for H2O2 in buffer) (BAHI and NECIB, 2015).

II.3.3.4. Reduced glutathione (GSH) assay

All mammalian tissues contain large amounts of reduced glutathione, sometimes referred to as γ-L-glutamyl-cysteinyl-glycine (GSH), a tripeptide that is highly concentrated in the liver. It protects cells from oxidative stress, facilitates xenobiotic detoxification, is critical in assessing the redox state of cells, and controls vital functions including cell division and apoptosis (LU, 2020). Glutathione is quantified using the protocol described by WECKBECKER and CORY (1988).

II.3.3.4.1. Principle

The technique measures the optical absorbance of 2-nitro-5 mercapturic acid, which is produced when glutathione's thiol (-SH) groups reduce 5,5'-dithio-bis-2-nitrobenzoic acid

(Ellman's reagent, DTNB). In order to do this, it is essential to deproteinize the homogenate in order to separate the glutathione-specific thiol groups (-SH) (KRIM, 2014).

II.3.3.4.2. Mode of operation

800 µl of homogenate and 200 µl of 0.25% salicylic acid are mixed together in a test tube. After giving the mixture a quick toss, refrigerated at 4°C for 15 minutes. 500 µl of supernatant is combined with 1000 µl of tris buffer (0.4 M tris, 0.02 M NaCl, pH = 8.9) and 25 µl of DTNB (0.01 M) after centrifugation at 1000 rpm for five minutes. The absorbance is measured at 412 nm after 5 minutes of incubation (WECKBECKER and CORY, 1988). Next, the concentration of GSH is determined using the following formula (KRIM, 2014), which is represented in µmole/mg of tissue (KHITHER, 2019).

II.3.3.4.3. Presentation of the findings

$$\mathbf{GSH = (OD \times 1 \times 1.525) / (13100 \times 0.8 \times 0.5 \times mg\ of\ tissue)}$$

- **DO:** Optical density.
- **1:** Total volume of solutions used in deproteinization (0.8ml homogenate + 0.2 ml of salicylic acid).
- **1.525:** Total volume of solutions used in the determination of GSH at the supernatant level (0.5 ml supernatant + 1 ml Tris + 0.025 ml DTNB).
- **13100:** Absorbance coefficient of the –SH group at 412 nm.
- **0.8:** Volume of the homogenate.
- **0.5:** Volume of the supernatant (KHITHER, 2019).

II.3.4. Histological sections

Following the procedures of fixation, dehydration and impregnation, embedding, cutting and deparaffinization, staining, and mounting, histological sections are prepared on each sample following sacrifice and dissection (BANCROF and GAMBLE, 2002).

II.3.4.1. fixation

Fixation attempts to harden the anatomical portion and preserve the structures in a condition as near to the life state as feasible by stopping all mitotic and enzymatic activity. For a duration of 24 to 48 hours, the samples are immediately fixed in 10% formalin (Photo 02). The samples are divided into minute pieces, which are subsequently immersed in consecutive alcohol baths in a unique box featuring perforated walls (ANDRE et al., 2008; DJOUDAD-KADJI et al., 2011).

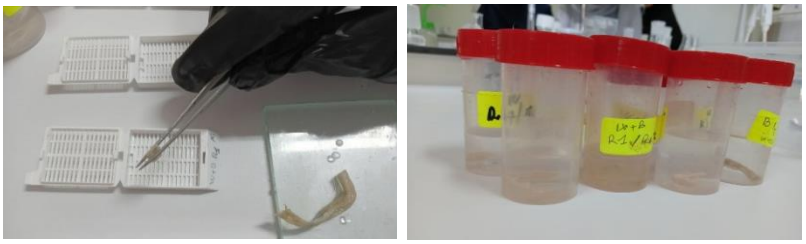


Photo 02. organ fixation (original photo).

II.3.4.2. Dehydration and impregnation

By eliminating intracellular water, dehydration aims to preserve the original cell structure at the moment of plasma membrane rupture. In order to dry the organ, the strips holding the samples are submerged in various alcohol baths utilising an automated circulation apparatus (ANDRE et al., 2008; DJOUDAD-KADJI et al., 2011).

II.3.4.3. Inclusion

After exiting the circulation apparatus, the tissue is extracted with forceps from the cassette and put straight into the inclusion equipment's metal mould filled with molten paraffin (Photo 03). To aid in destruction, it is then filled with paraffin and moved to a cooling plate. This step's objective is to enable the creation of regular, thin and 3 µm thick pieces so that they can be examined under a microscope (ANDRE et al., 2008; DJOUDAD-KADJI et al., 2011).

Photo 03. Organ tissue inclusion stage (original photo).

II.3.4.4. Preparation of a histological section

Using a microtome, the paraffin blocks are thinly sliced following the embedding process (Photo 04). After being stretched out in a 45°C water bath to loosen them, the portions are put on glass slides. After setting them on metal slide holders, they are dried for about an hour at 40°C in the oven (ANDRE et al., 2008; DJOUDAD-KADJI et al., 2011).

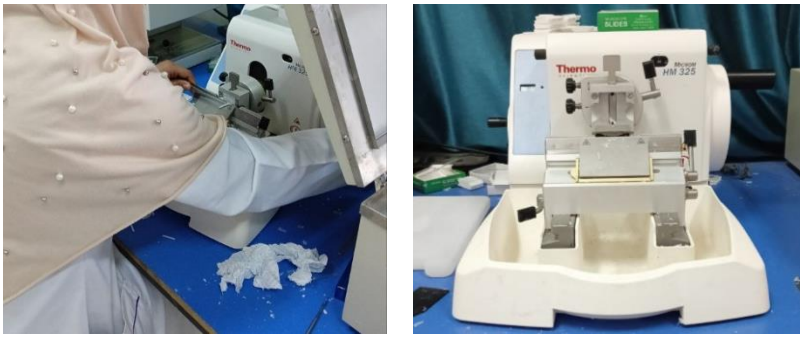


Photo 04. paraffin blocks cutting into thin slices using a microtome (original photo).

II.3.4.5. Coloration

The slides are put straight into several stain-ready trays. This stage lasts for sixty-seven minutes and goes like this:

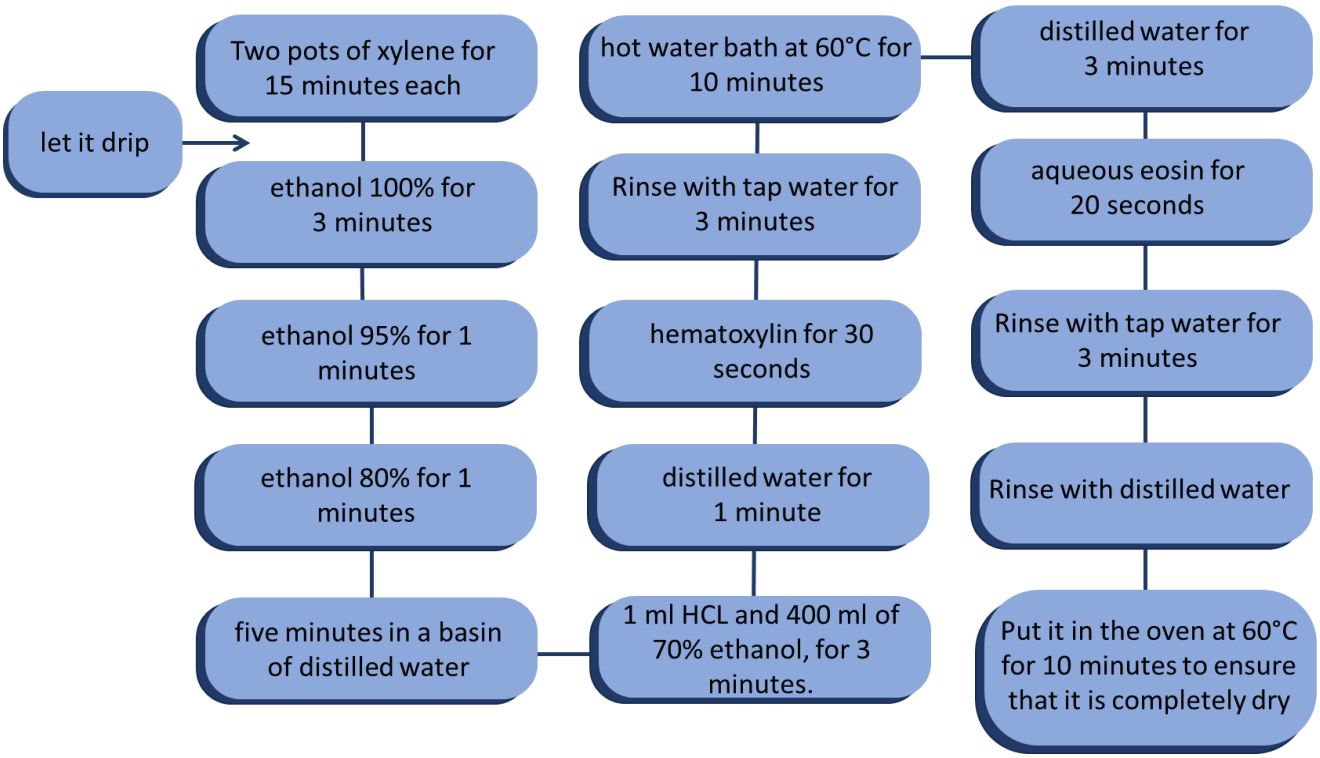


Figure 09. Coloration stages (DJOUDAD-KADJI *et al*., 2011 ; ANDRE *et al*., 2008).

II.3.4.6. Assembly and microscopic observation

A histology slide is now prepared and ready to be examined under a microscope. To guarantee clear vision, a few drops of synthetic glue should be carefully fitted to the stained slide

before adding them to the coverslip. This will help to prevent air bubbles. The slides are thereafter allowed to dry (DJOUDAD-KADJI et al., 2011; ANDRE et al., 2008). and proceeded to use an optical microscope with magnifications of x40 and x10 for observation.

II.3.5. Bacteria identification test

Use 145 ml of the ID suspension for the Gram-negative card and 280 ml for the Gram-positive card. The ID test card should first be taken out of its foil pouch and allowed to come to room temperature. To prevent unintentional touch, insert the card into the cassette with the transfer tube facing away from you. Mark the upper part of a transparent polystyrene tube measuring 12 by 75 mm with the unique identification details of every specimen.

3.0 milliliters of saline are added to the tube using the dispense set. Using a sterile stick or swab, transfer colonies with comparable morphology to the saline tube and thoroughly mix to form a homogenous mixture. Use the Density Check Plus to confirm that the inoculum density matches the McFarland unit specified on the ID card. Before placing the tube into the Density Check Plus and spinning it 360 degrees, clean the outside of the tube with lens paper or lint-free tissue. After resetting the device using a saline tube, measure turbidity using a diagnostic tube. Verify that the McFarland unit in display is within the permitted range. Recheck after diluting the suspension with a tiny amount of saline if the unit is too high. If it is too low, add more organisms and recheck the density.

Once the density is correct, place the inoculum tube in the well in front of the ID card. Follow the same steps for the AST card, noting that the ID card has a blue transfer tube, while the AST card has a gray transfer tube. The sealed test kits are then automatically moved into the VITEK 2 device, where they incubate and analyze the samples.

Photo 05. Preparing samples for identifying bacteria using the VITEK 2 device (original photo).

CHAPTER III

Results and discussion

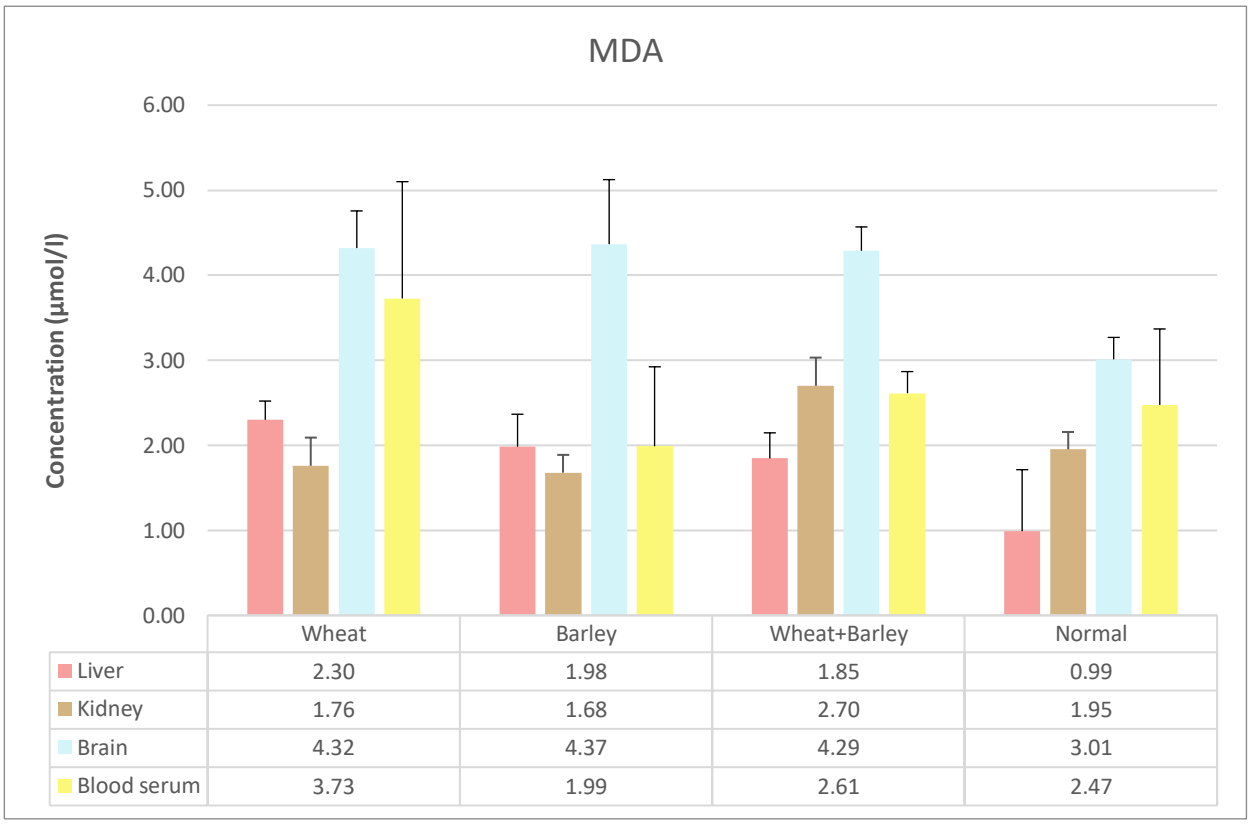
In this chapter, the biological activities tested for are aimed at evaluating the effects of wheat and barley on oxidative stress parameters, tissue structure, and gut microbiota in Wistar albino rats.

III.1. Biological activities *in vivo*

III.1.1. Effects on oxidative stress parameters

In the context of this growing health-conscious trend, our study focuses on evaluating the impact of wheat and barley-derived prebiotics on gut microbiota and overall health in albino Wistar rats. Wheat (Triticum aestivum) and barley (Hordeum vulgare) were specifically chosen as prebiotics, and their biological effects were assessed in vivo. Trillions of commensal bacteria, including around 1000 species, are present in the gastrointestinal (GI) tract and are essential for preserving the functions of the membrane barrier and controlling the metabolic processes of the host organisms (Morais et al., 2020; Ji et al., 2015). Prebiotics have a significant impact on host well-being because of their wide range of advantageous effects on host health, which include increased mucosal and systemic immunity, improved resistance to pathogenic bacterial colonization, and enhanced systemic immunity (Tuohy et al., 2003; Spiller, 2008; Cummings & Macfarlane, 2002; Bruzzese et al., 2006; Choct, 2009; Watzl et al., 2005; Hosono et al., 2003). For example, gut bacteria may digest dietary fiber to produce short-chain fatty acids (SCFAs), which have been demonstrated to control neuroplasticity in the central nervous system and improve depressed behavior in animal models (Dalile et al., 2019). Variations in the diversity and balance of microbiota go beyond the gastrointestinal tract and affect several target organs as well as the immune system by modifying intestinal mucosa permeability, which is often known as "leaky gut" syndrome (Vajro et al., 2013; De Goffau et al., 2014). Reactive oxygen species (ROS) produced by mucosa-resident cells or recruited innate immune cells play crucial roles in antimicrobial responses and signaling pathway regulation. The diverse cell types of the intestine respond to commensal microbiota or pathogens with immune tolerance or proinflammatory signals, respectively (Sartor, 2008; Aviello & Knaus, 2016). At stable levels, ROS perform essential biological tasks such as inducing innate immune responses and protecting against oxidative stress, even if excessive levels can lead to cellular malfunction and biomolecular damage (Sun et al., 2020; Angelova & Abramov, 2018). According to several studies, oxidative stress, which results from an imbalance between ROS and antioxidant levels, is linked to a number of neurological disorders by interfering with redox signaling pathways and causing cellular damage (Kulbacka., 2009; Halliwell, 2007; Sun et al., 2020).

III.1.1.1. Effects on malondialdehyde (MDA) levels

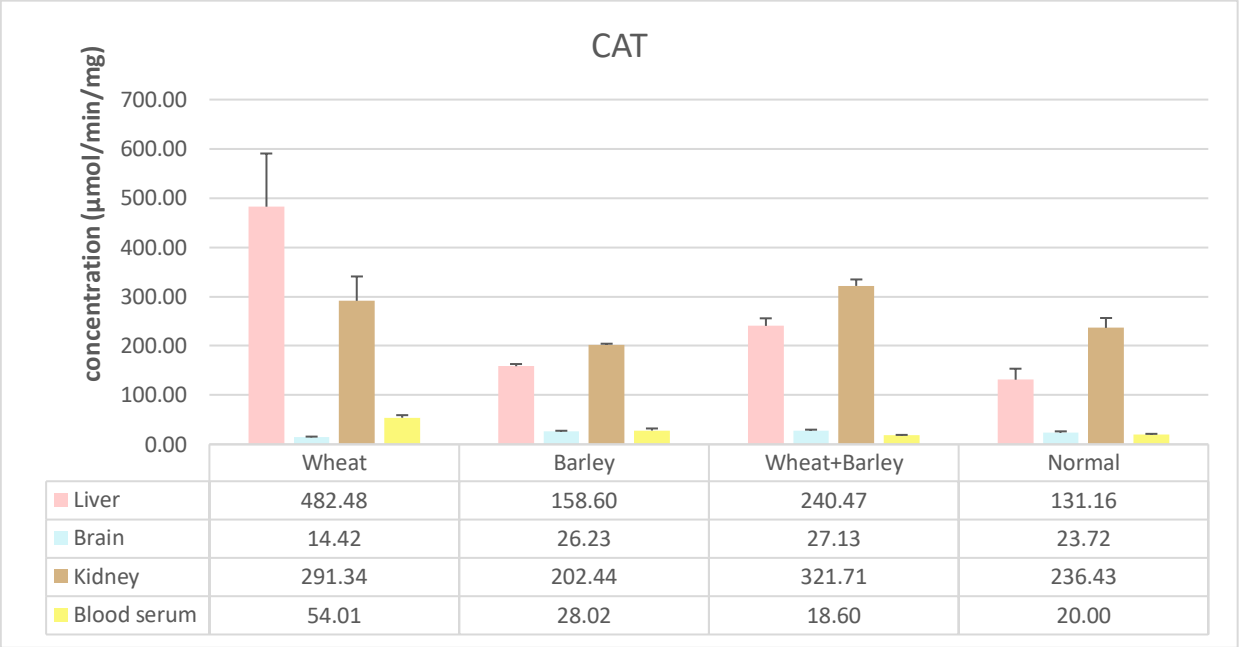


	Wheat	Barley	Wheat+Barley	Normal
Liver	2.30	1.98	1.85	0.99
Kidney	1.76	1.68	2.70	1.95
Brain	4.32	4.37	4.29	3.01
Blood serum	3.73	1.99	2.61	2.47

Figure 10. MDA levels in the liver, kidneys, brain, and blood of rats from the four groups.

The MDA levels in the blood of the different batches and different organs (liver, kidney, and brain) are shown in Figure 10. Following consumption of high-prebiotic meals (wheat and barley, wheat and barley mixture), the rats in the wheat (2.30±0.22 µmol/l) and barley (1.98±0.38 µmol/l) groups, as well as the wheat+barley (1.85±0.30 µmol/l) groups, showed significantly higher hepatic MDA levels than those in the normal batch (0.99±0.72 µmol/l). The findings also show that rats from the wheat+barley batch had higher renal MDA levels (2.70±0.33 µmol/l) than rats from the normal batch (1.95±0.20 µmol/l). Additionally, rats from the wheat batch (1.76±0.33 µmol/l) and barley batch (1.68±0.21 µmol/l) had lower renal MDA levels than those from the normal batch. Additionally, compared to the normal group (3.01±0.26 µmol/l), the brain exhibits greater MDA levels for wheat, barley, and wheat barely combination (4.32±0.44µmol/l), (4.37±0.76 µmol/l), and (4.29±0.28 µmol/l), respectively. Furthermore, compared to the normal group (2.47±0.0.89 µmol/l), the wheat group rats had a higher MDA level in their blood (3.73±1.37 µmol/l). where when compared to the normal batch, the wheat barely batch exhibits a slight increase (2.61±0.25 µmol/l). Similarly, the blood MDA levels of the barley group were found to be lower than those of the normal group (1.99±0.93 µmol/l).

III.1.1.2. Effects on catalase activity (CAT) levels

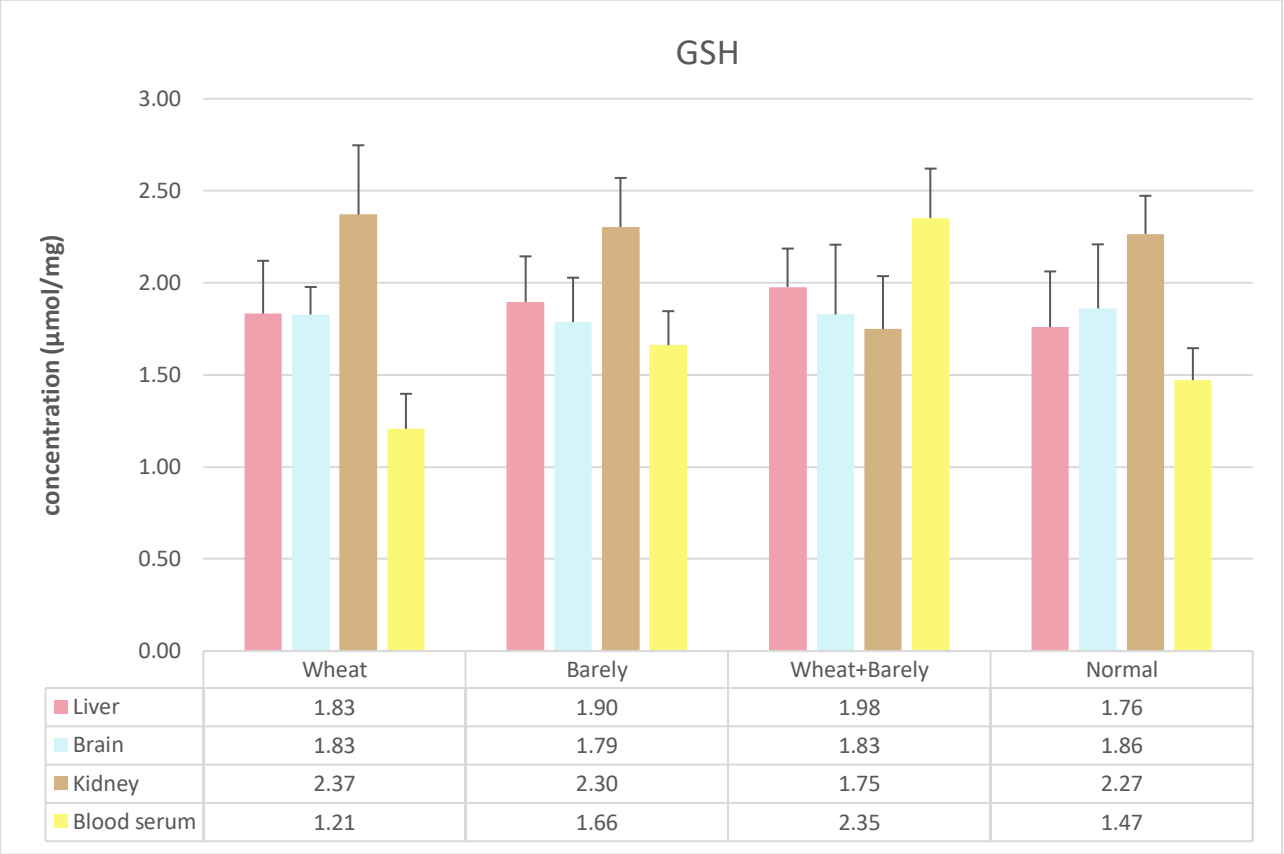


	Wheat	Barley	Wheat+Barley	Normal
Liver	482.48	158.60	240.47	131.16
Brain	14.42	26.23	27.13	23.72
Kidney	291.34	202.44	321.71	236.43
Blood serum	54.01	28.02	18.60	20.00

Figure 11. CAT levels in the liver, kidneys, brain, and blood of rats from the four groups

Figure 11. displays the CAT levels in the blood of the various batches and organs (liver, kidney, and brain). After consuming meals high in prebiotics (wheat and barley, or a combination of wheat and barley), Rats in the wheat group had a significantly higher hepatic CAT activity (482.48±108.01 µmol/min/mg) than those in the normal group (131.16±22.38 µmol/min/mg). Rats from the barley group exhibit a little increase in hepatic CAT activity (158.60±4.41 µmol/min/mg) as compared to the normal group. Furthermore, in comparison to the natural group, the mixed group showed a considerable increase (240.47±15.40 µmol/min/mg). Rats in the wheat group showed blood serum CAT activity that was substantially higher than that of the normal group (20±1.27 µmol/min/mg) at (54.01±5.23 µmol/min/mg). When compared to the normal group, the blood serum CAT activity of the barley group's rats is significantly higher (28.02±4.18 µmol/min/mg). Furthermore, the mixed group's result (18.60±0.55 µmol/min/mg) was somewhat lower than that of the natural group. It is also noteworthy that the brain CAT activity of the rats in the mixed group (27.13±2.63 µmol/min/mg) and barley group (26.23±1.34 µmol/min/mg) were greater than those in the normal group (23.72±2.66 µmol/min/mg). Moreover, the wheat group displayed a lower value (14.42±1.30 µmol/min/mg) compared to the natural group. Furthermore, we observe that the Kidney values of the barley group (202.44±1.87 µmol/min/mg) are marginally lower than those of the normal group (236.43±20.11µmol/min/mg), whereas the mixed group (321.71±13.06µmol/min/mg) and Wheat group (291.34±49.51µmol/min/mg) are substantially higher than the normal group.

III.1.1.3. Effects on reduced glutathione (GSH) levels



	Wheat	Barely	Wheat+Barely	Normal
Liver	1.83	1.90	1.98	1.76
Brain	1.83	1.79	1.83	1.86
Kidney	2.37	2.30	1.75	2.27
Blood serum	1.21	1.66	2.35	1.47

Figure 12. GSH levels in the liver, kidneys, brain, and blood of rats from the four groups.

Hepatic GSH levels show an almost high increase in the mixed group (1.98±0.21 µmol/mg) and barley group (1.90±0.25 µmol/mg) when compared to the normal group (1.76±0.30 µmol/mg). In the wheat group, there was a little amount of rise (1.83±0.29 µmol/mg) when compared to the normal group as shown in fig12. Additionally, we see that the brain values of the normal group (1.86±0.35 µmol/mg) are very slightly higher than those of the barley group (1.79±0.24µmol/mg), wheat group (1.83±0.15 µmol/mg), and mixed group (1.83±0.38µmol/mg). Furthermore, we observe that the blood serum values of the wheat group (1.21±0.19 µmol/mg) are marginally lower than those of the normal group (1.47±0.17 µmol/mg), while the mixed group (2.35±0.27 µmol/mg) and barley group (1.66±0.18 µmol/mg) are higher than those of the normal group. Moreover, we note that the wheat group (2.37±0.38 µmol/mg) and barley group (2.30±0.27 µmol/mg) have greater kidney values than the normal group (2.27±0.21 µmol/mg). however, the kidney values of the Wheat+Barely group (1.75±0.29 µmol/mg) is lower.

Giving barley diet leads to an increase in MDA in the liver and brain (figure 10). Barley contains omega 3 and omega 6 (Al-Taher & Nemzer, 2023), they are called polyunsaturated fatty acid (Saini et al., 2021). (PUFA)Polyunsaturated fatty acids (PUFAs) are a family of lipids having two or more double boundaries that are major substrates for lipid peroxidation. Lipid peroxidation or reaction of oxygen with unsaturated lipids produces a wide variety of oxidation products, malondialdehyde (MDA) is one of the numerous distinct aldehydes that can arise as secondary products during lipid peroxidation. Because MDA reacts well with thiobarbituric acid (TBA), it has been used extensively for many years as a simple biomarker for lipid peroxidation of omega-3 and omega-6 fatty acids (Ayala et al., 2014). ARA (ω-6) and DHA (ω-3) are the most prevalent PUFA in the brain, making up about one fifth of its dry weight (Bentsen, 2017). The brain makes up 50% of its dry weight in lipids, which is the second-highest amount after adipose tissues (Hornemann, 2021). The liver contains linoleic acid (Salem et al., 2015), liver is the center of fatty acid synthesis and lipid circulation through lipoprotein formation, and it plays a major role in lipid metabolism (Nguyen et al., 2008). It also showed an increase in GSH (figure 12) and CAT (figure 11). Barley contains β-glucan, a polysaccharide that takes the form of fiber (Kim et al., 2006), which mainly contains β-(1,3-1,4)-D-glucan. β-Glucan found to possess significant antioxidant activity (Kofuji et al., 2012). Values were normal for kidney and blood serum.

Giving wheat diet leads to an increase in MDA in liver, brain, blood serum (figure 10). Wheat contains PUFA (omega 3, omega 6) more than barley (Al-Taher & Nemzer, 2023), Which leads to lipid peroxidation and production MDA (Ayala et al., 2014). it also showed an increase in GSH and CAT values (figure 11) in general, as wheat contains antioxidants, for example wheat bran contains antioxidants and can exert its effects by promoting scavenging of radicals, chelation of metal ions, and the activation of antioxidant enzymes (Higuchi, 2014), wheat germ (protein, polysaccharide) also has antioxidant capacity. It reduces liver and blood serum MDA and increases liver CAT in cases of high fat (Liu et al., 2022). The values were normal for the kidney.

Giving wheat and barley (the mixed group) diet leads to an increase in MDA in the liver, brain and kidney compared to the normal group, the blood serum values was almost similar, and its values MDA were lower compared to the wheat group and the barley group (figure 10), as the effect of wheat germ appeared in reducing the liver MDA in the mixed group compared to the wheat group and the barley group (Liu et al., 2022), and wheat also increased the MDA in Blood serum. It also showed an increase in GSH and CAT compared to the three groups in general, as the effect of wheat germ on the increase in liver CAT appeared, and it also showed an antioxidant

capacity in blood serum (Liu et al., 2022). Cooperation between antioxidants in wheat and barley slightly improved brain GSH and CAT, and improved blood serum GSH and kidney CAT.

In summary, the findings suggest that the inclusion of barley, wheat, and their combination in the diet significantly influences oxidative stress markers and antioxidant enzyme activities, with each having distinct impacts on different organs. The combined diet of wheat and barley appears to offer a synergistic benefit, improving certain oxidative stress parameters and enhancing overall antioxidant defenses more effectively than either alone.

III.1.2. bacteria identification

Table 03. Identification of Bacteria Isolated from the Large Intestine of Rats Fed Different Diets.

bacteria species	Wheat	Barely	Normal	Wheat Barely
Staphylococcus vitulinus (GP)	+	+	+	-
Leuconostoc mesenteroides ssp cremoris (GP)	-	-	-	+
Staphylococcus auricularis (GP)	-	-	-	+
Staphylococcus lentus (GP)	-	-	-	+
Pantoea spp (GN)	-	+	-	-

III.1.2.1. Leuconostoc

Leuconostoc mesenteroides subsp. cremoris, an obligate heterolactic fermentative lactic acid bacterium extensively used in commercial dairy fermentations (Özcan et al., 2019), is particularly well-suited to sugary habitats and possesses a broad range of biocatalytic capabilities beneficial in carbohydrate modification and synthesis (Soetaert et al., 1995); few studies have revealed its significant promise as a probiotic strain (Kekkonen et al., 2008), with Benmechernene et al. (2013) finding it superior to the probiotic *Lactobacillus* strain currently in clinical use for cytokine production, while also demonstrating its ability to survive relatively high salt and sugar concentrations, create CO2 and acids that reduce pH and inhibit the growth of rotting microbes, and produce an anaerobic environment favorable for subsequent Lactobacillus spp. growth (Fellows, 2017); furthermore, it can inhibit pathogen growth, serve as a safe probiotic for future research (Hamad et al., 2021; Del Carmen Casado Muñoz et al., 2014), and has high antibacterial activity against both gram-positive and gram-negative bacteria (Bajpai et al., 2016), including S. pyogenes (Zoumpopoulou et al., 2020) and G. anatis (Zhang et al., 2021).

Several studies have found that *Leuconostoc mesenteroides* bacteria can be isolated from wheat and barley, which explains their presence in the wheat-barley group (Çakır et al., 2020; Harth et al., 2016; Manini et al., 2016; Alfonzo et al., 2013; Robert et al., 2006; Vaughan et al., 2001).

III.1.2.2. Staphylococcus

Many Gram-positive bacteria that belong to the family *Staphylococcaceae*, order *Bacillales*, class *Bacilli*, and phylum Firmicutes are taxonomically grouped under the genus *Staphylococcus*. The genus *Staphylococcus*, which belongs to the complex family *Staphylococcaceae*, has more than 40 known species, *including S. auricularis and S. sciuri*. According to Liu (2015), *S. sciuri* contains *S. fleurettii, S. lentus, S. sciuri, S. stepanovicii, and S. vitulinus*.

Staphylococcus sciuri is a coagulase-negative, novobiocin-resistant, and oxidase-positive staphylococcal strain. The organism is classified as an animal bacterial species, and it is widely found on the skin and mucosal surfaces of a variety of pets, agricultural and wild animals (Hauschild & Schwarz, 2003; Kloos, 1980; Kloos et al., 1997), (Stepanović et al., 2001), as well as in animal-derived food (Papamanoli et al., 2003; GarcíA et al., 2002). It is also found in environmental reservoirs such soil, sand, water, and marsh grass (Kloos, 1980). *S. sciuri* can colonize people and has low carrier rates in the nasopharynx, skin, and urogenital tract (Stepanović et al., 2005; Stepanovic et al., 2003; Couto et al., 2000). The clinical importance of *S. sciuri* in humans appears to be rising, as the bacterium has been linked to a variety of illnesses, including endocarditis (Hedin & Widerström, 1998), peritonitis (Bo, 2000), and septic shock (Horii et al., 2001).

S. lentus is a coagulase-negative *staphylococcus* from the *Staphylococcus sciuri* group, which comprises *S. sciuri, S. lentus, and S. vitulinus*. Those *staphylococci* are recognized as animal infectious agents and have been identified in rats, chicks, animals, agricultural soil, and water (Stepanovic et al., 2005). *S. sciuri* may colonize humans and produce serious infections, such as endocarditis septic shock, urinary tract infection, wound infections, endophthalmitis, and pelvic inflammatory disease (Dakic et al., 2005).

Staphylococcus auricularis frequently colonizes the external ear canal and its surrounding areas. It is seldom pathogenic and has only been linked to a few skin and soft tissue infections (De Luca et al., 2022; Natsis & Cohen, 2018). *Staphylococcus auricularis* and *Staphylococcus capitis* dominate the microflora of human ears, particularly the external ear (external auditory meatus) (Kloos, 1982). according to Kloos & Schleifer in 1983 Of the 25 individuals sampled, 23 (92%)

had *S. auricularis* populations in the external auditory meatus. In 22 of the 23 individuals, *S. auricularis* was the most common *Staphylococcus* species found in this place. In a 1998 investigation, Akiyama et al. found *S. auricularis* in two infected cysts out of 18 cysts cultivated.

The presence of *Staphylococcus* bacteria in rat's intestines can be related to exposure to contaminated sawdust or through other rate's hair, where licking behavior facilitates transmission. Given the presence of *Staphylococcus auricularis* bacteria in the external ear (Kloos & Schleifer, 1983), one mouse licking another's ear may encourage the transfer of these germs to the intestines.

III.1.2.3. Pantoea spp

The bacterial genus *Pantoea*, a non-encapsulated, non-spore-forming, anaerobic Gram-negative bacillus belonging to the family *Enterobacteriaceae*, is associated with plants and has beneficial effects on plant development and health, particularly in wheat and barley under harsh conditions (Soluch et al., 2021; Suman et al., 2020; Kaur et al., 2020; Rahman et al., 2018; Braun-Kiewnick et al., 2000). thus, explaining their presence in the barley group. While *Pantoea* is not an obligate infectious agent in humans, it can cause opportunistic infections, primarily through wound contamination with plant material or as a hospital-acquired infection in immunocompromised individuals (Dutkiewicz et al., 2016). Additionally, Japanese scientists discovered that wheat flour extract exhibits anti-tumor effects due to the presence of *Pantoea agglomerans*. They isolated and purified the active substance, a low-molecular-mass (5 kDa) lipopolysaccharide (LPS) of P. agglomerans, known as 'LPSp' or 'Immunopotentiator from *Pantoea agglomerans* 1 (IP-PA1)' (Hebishima et al., 2011; Soma et al., 2008; Kohchi et al., 2006; Iwamoto et al., 1996; Kasugai et al., 1995; Nishizawa et al., 1992). Mizuno and Soma (1992) described this preparation as a 'nontoxic type of Coley's toxin,' potentially useful for treating cancer and multiple intractable diseases via oral or percutaneous routes without side effects.

The only beneficial bacterium we detected is Leuconostoc mesenteroides ssp. cremoris. The remaining bacteria are contaminants, commonly found in soil, wheat and barley seeds, the surfaces of rat's fur, or their external ears. This contamination could result from improper handling methods, insufficient cooking of wheat and barley, or rats licking each other, facilitating the transfer of bacteria into their intestines. Despite these limitations, numerous studies affirm the potential of prebiotics to enhance the composition and activity of beneficial bacteria such as Lactobacillus and Bifidobacterium populations.

Research has demonstrated that prebiotics significantly boost Bifidobacterium populations in the colon of adults (Tandon et al., 2019; Holscher et al., 2015; Costabile et al., 2010). An increase in Bifidobacterium abundance is often regarded as a critical indicator of prebiotic efficacy

(Scott et al., 2014). Prebiotics alter the gut microbiota composition by increasing the quantities of bifidobacteria and lactobacilli, while concurrently reducing toxin-producing bacteria such as Bacteroides, proteolytic clostridia, and Escherichia coli (Ogueke et al., 2010).

Everard et al. (2014) discovered significant changes in the fecal microbiota of rats treated with prebiotics, observing increases in genera such as Akkermansia, Dehalobacterium, Prevotella, Sutterella, and Tannerella, while noting decreases in Alistipes, Allobaculum, Clostridium, Coprobacillus, Coprococcus, Eubacterium, Faecalibacterium, and Ruminococcus. Similarly, Akkermansia, Bifidobacterium, and Sutterella were undetectable in high-fat diet rats but reappeared following prebiotic treatment, indicating their role in gut microbiota modulation.

Weiss et al. (2015) found significant variations in bacterial groups between pigs fed barley and wheat diets. Barley-based diets improved microbial composition, demonstrated by a higher ratio of Lactobacillus spp. to Enterobacteriaceae in both ileal digest and feces. Wheat-based diets, on the other hand, increased the abundance of beneficial ileal Roseburia spp. and fecal Bifidobacterium spp. Tako et al. (2014) further showed that prebiotics naturally present in wheat grains and bread products significantly enhanced the population of intestine-beneficial bacteria in Fe-deficient broiler chicks, with higher prebiotic concentrations leading to more bifidobacteria.

Moreover, studies have shown that barley consumption positively correlates with an increase in beneficial bacteria such as Bifidobacterium and Butyricicoccus (Matsuoka et al., 2022). Martínez et al. (2012) noted that increasing gut bacteria diversity led to a rise in Blautia. A Swedish study found that barley consumption increases the ratio of Prevotella/Bacteroides and enhances host blood glucose metabolism (Kovatcheva-Datchary et al., 2015). Nilsson et al. (2010) also reported that barley consumption impacts gut microbes and host health positively. These findings imply that barley and wheat may favorably affect gut flora composition and host metabolic health, reinforcing the potential health benefits of including these prebiotics in the diet.

III.1.3. Histological section

We observed in Figure 13 a significant increase in total wall thickness in the colon of rats fed on wheat+barley (258.80µm) and barley (192.77µm) compared to the normal group (133.32µm), with differences of 125.48µm and 59.45µm, respectively. Particularly for the wheat+barley diet, the difference is very pronounced. Conversely, rats fed on wheat alone (119.62µm) showed a noticeable decrease in wall thickness, with a difference of 13.7µm compared to the normal group.

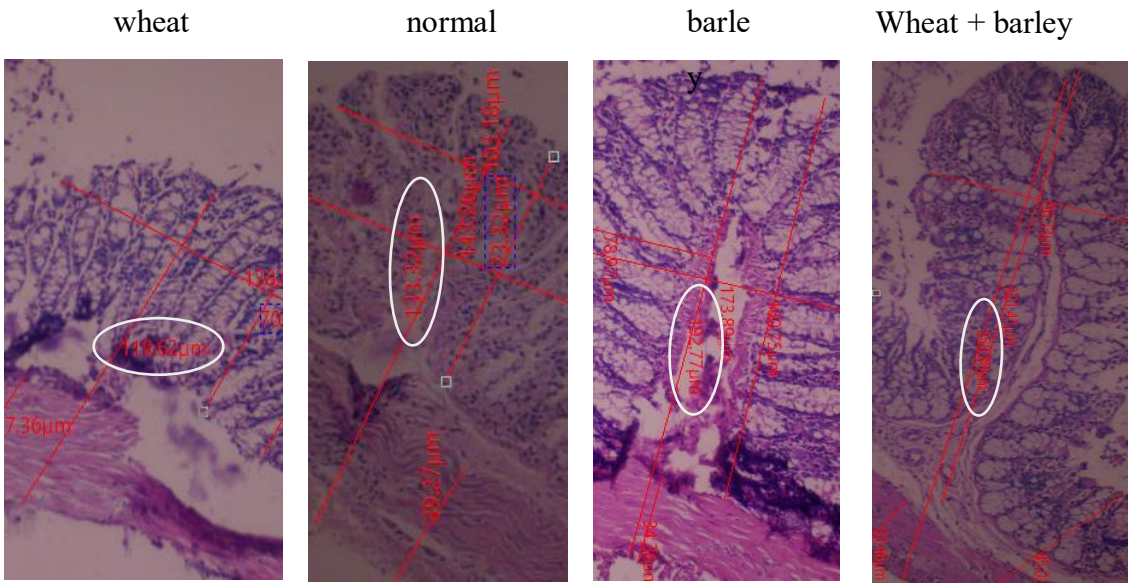


Figure 13. Photomicrographs showing total wall thickness in colon of rat (×100).

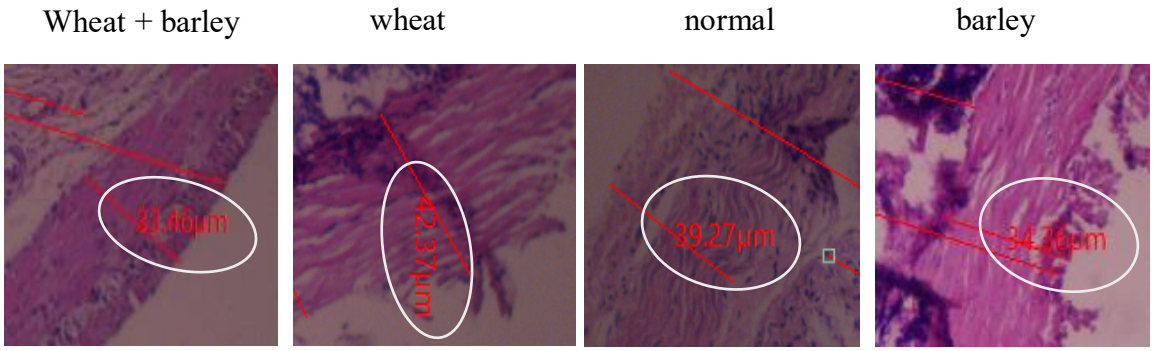


Figure 14. Photomicrographs showing muscle tunic thickness in colon of rat (×100)

We observed in Figure 14 that the muscle tunic thickness in the colon of rats fed on wheat (42.37µm) is greater than in the control group (39.27µm), with a difference of 3.1µm. In contrast, rats fed on barley (34.36µm) and the wheat-barley mixture (33.46µm) showed a noticeable decrease in muscle tunic thickness, with differences of 4.91µm and 5.81µm, respectively, compared to the control group.

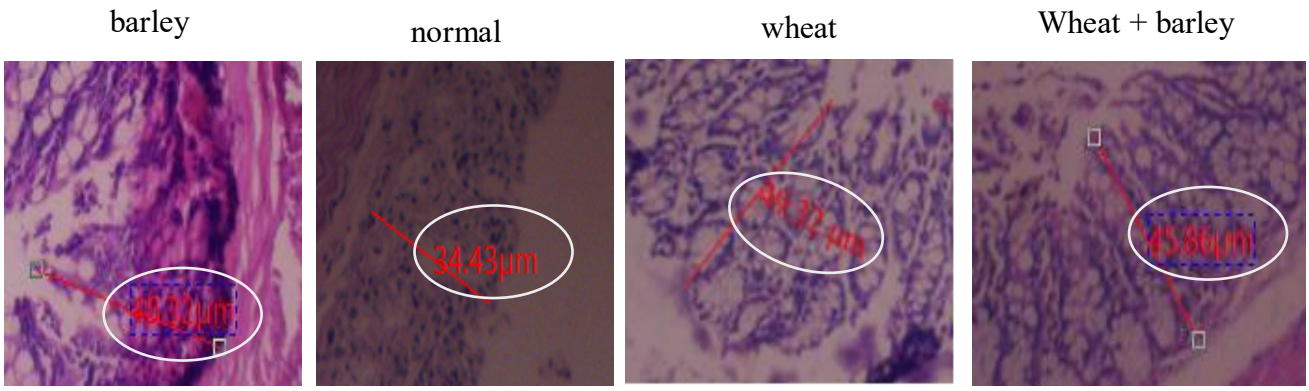


Figure 15. Photomicrographs showing mucosa tunic thickness in colon of rat (×100)

We observed that the mucosa tunic thickness in the colon of rats fed on wheat (49.32µm), barley (48.32µm), and the wheat-barley mixture (45.86µm) is greater than that of the control group (39.27µm), with differences of 14.89µm, 13.89µm, and 11.43µm, respectively.

Our study found that rats given a wheat diet had higher muscular tunic thickness in the colon (42.37 µm) than the control group (39.27 µm). Wheat-fed rats had thicker mucosa tunics compared to the control group (34.43 µm). However, the total wall thickness decreased significantly by 13.7 µm compared to the control group (133.32 µm). Additionally, rats fed a barley diet showed a decrease in muscle tunic thickness in the colon (34.36 µm) compared to the control group (39.27 µm). The barley-fed rats had higher mucosa tunic thickness (48.32 µm) compared to the control group (34.43 µm). The total wall thickness increased significantly by 59.45 µm compared to the control group (133.32 µm). In rats given a wheat-barley mixture, the muscle tunic in the colon was smaller (33.46 µm) compared to the control group, whereas the mucosa tunic thickness and overall wall thickness were greater than the control group. We observed variations in the results for barley and the wheat-barley mixture which is consistent with Kerss et al. (1982) noted significant variations in mucus thickness not only within the same species but also within different regions of the same mucosal section. This emphasizes the inherent variability in measuring mucus thickness and underscores the need for careful consideration of factors such as methodology and sample variation when interpreting research findings. Overall, there was an increase in the total wall thickness of the colon in rats fed these diets compared to those fed wheat alone, which did not show an increase in total wall thickness. However, the wheat diet did result in increased thickness in other parts of the colon. According to these data, wheat has a variable effect on colon wall thickness. This is consistent with the findings of Jacobs & White (1983) and

Jacobs & Schneeman (1981), who found that dietary wheat bran modulates colonic mucosal cell proliferation based on the anatomical area of the colon. Dongowski et al. (2002) discovered that barley-rich diets led to greater levels of resistant starch and β-glucan in the intestines. This resulted in significantly higher amounts of short-chain fatty acids (SCFA) in the cecum and colon, contributing to their increased mass. also, Aoe et al. (2019) found that Barleymax (BM) increased the levels of total short-chain fatty acids (SCFAs) in the distal colon. In addition, Lim et al. (2019) showed that oral administration of 100–300 mg/kg of fermented barley extracts (FBe) resulted in significant laxative effects. This was evidenced by improvements in intestinal charcoal transit ratio and increased thicknesses of colonic mucosa. Moreover, Hedemann et al. (2009) discovered that several forms of non-digestible carbohydrates (NDCs), including barley hulls, impact the thickness of the mucus layer in the gut. Unlike Whiteley et al. (1996) He came to that Total mucosal volume was not correlated with the concentration of total SCFA or butyrate in the colon. These findings show that diet-induced changes in colonic mucosal development, as evaluated by total mucosal volume, are positively linked with fecal weight but not with colonic fermentation. aligning with the findings of Wyatt et al. (1988) and Zhang and Lupton (1994). This contradicts the hypothesis suggesting that dietary fiber-induced alterations in colonic fermentation primarily mediate colonic mucosal growth in the normal colon (Sakata, 1984). There seems to be a fundamental disparity in the study designs between those demonstrating enhanced mucosal growth in response to SCFA and those that do not. The majority of studies showing a positive effect of SCFA on mucosal growth involve administering SCFA solutions directly into the large intestine through methods such as ileal fistula, indwelling colonic catheter, or indwelling cecal catheter, often in animals fed a low-residue diet or receiving parenteral nutrition (Frankel et al., 1994; Friedel & Levine, 1992; Kripke et al., 1989; Sakata, 1989; Sakata, 1986; Sakata, 1984). Furthermore, in these studies, there are significant variations in the magnitude of the response and inconsistencies among different measures of mucosal growth. For example, Kripke et al. (1989) found that compared to saline, the infusion of mixed SCFAs into the colon of vasectomized rats resulted in an 82% increase in proximal colonic DNA content and a 16% increase in mucosal thickness, but no change in mucosal weight, protein, or RNA. Friedel and Levine infused a similar SCFA solution into rats receiving total parenteral nutrition and found a 30% increase in DNA and a 38% increase in mucosal height, but no change in mucosal weight or protein (Friedel & Levine, 1992). Frankel et al. observed that cecal infusion of SCFA into rats did not stimulate cell proliferation in the proximal colon, but direct colonic infusion did (Frankel et al., 1994). Conversely, Sakata found that SCFA infusion into the large intestine without direct exposure to the proximal colon could induce cell proliferation in the proximal colon (Sakata, 1986). In

addition, we found that our measured colon thickness in rats was notably smaller compared to findings from other studies. For instance, Atuma et al. (2001), utilizing the micropipette technique with intravital microscopy, reported a mean thickness of colon mucus at 830 ± 110 μm. Similarly, El-Salhy et al. (2013) observed that the maximum thickness of the rat colon wall was 0.35 mm, which translates to 350 μm.

The observed smaller colon thickness in our study could be attributed to the limitations of standard histological methods. These methods involve the use of organic fixatives, extensive dehydration, and paraffin embedding, which often result in significant shrinkage of the adherent mucus layer and sometimes its complete loss from the mucosal surface (Allen & Pearson, 2000; Allen, 1989).

For instance, in studies employing modified unfixed section techniques, reported values for the rat stomach, cecum, and colon mucus thickness were 39, 18, and approximately 20 μm, respectively (Rubinstein & Tirosh, 1994). However, when celloidin fixation of cryostat sections was utilized, approximate mucus thickness values for the rat duodenum, jejunum, ileum, and proximal colon were 28, 93, 101, and 53 μm, respectively (Szentkuti & Lorenz, 1995).

Recent histological methods for cryostat sections, which minimize shrinking of the adhering mucus gel layer, revealed values for mucus thickness in the rat antrum, corpus, and colon of 166, 184, and 45 μm, respectively (Strugala et al., 1999; Jordan et al., 1998). These variations in measurement techniques and fixation methods highlight the importance of considering methodology when interpreting colon thickness results.

The study demonstrates a significant interplay between oxidative stress parameters, tissue histology, and gut microbiota composition in Wistar albino rats fed a diet enriched with wheat and barley combined with mabroma. Elevated malondialdehyde (MDA) levels indicate increased lipid peroxidation due to oxidative stress. However, the concurrent rise in catalase (CAT) and glutathione (GSH) activities suggests a robust antioxidant defense response to neutralize reactive oxygen species (ROS). The presence of omega-3 fatty acids in wheat and barley likely contributes to this antioxidant activity, enhancing the body's defense against ROS and mitigating oxidative damage (Al-Taher & Nemzer, 2023; Mansouri et al., 2021; Heshmati et al., 2019). This antioxidant activity and omega-3 FAs helps prevent lipid peroxidation (Li et al., 2023; Heshmati et al., 2019; Valgimigli & Pratt, 2012; Burton & Ingold, 1986), which potentially enhances colon thickness. Thus, histological analysis revealed a notable increase in colon thickness in the groups fed with wheat, barley, and the wheat-barley mixture, likely due to the beneficial effects of omega-3 fatty

acids, which have been shown to promote mucosal integrity and cellular repair processes (Köstek et al., 2024).

However, the inclusion of mabroma in the diet, particularly its components like soy and corn oil, could modulate these effects. Soy, which constitutes a significant portion of mabroma, has been reported to cause colon tissue damage in high concentrations, although the resistant starch present in wheat and barley might mitigate this damage (Toden et al., 2007). On the other hand, corn oil is known to increase oxidative damage, potentially explaining the heightened oxidative stress markers (Domitrovic et al., 2006).

The bacterial examination did not identify specific beneficial bacteria such as Bifidobacterium and Lactobacillus, but the presence of the probiotic bacterium Leuconostoc mesenteroides can impact the mechanism of the intestinal barrier via regulating the regeneration of intestinal epithelial cells. Numerous studies, including Lim et al. (2019), have shown that probiotics increase the production of tight junction proteins and mucin secretion while promoting the immune system. The omega-3 fatty acids in wheat and barley might create a more favorable gut environment, enhancing the antioxidant response and supporting mucosal health (Köstek et al., 2024), despite the presence of contaminants likely introduced through improper handling, insufficient cooking of wheat and barley, or inter-animal contamination among the rats. These findings underscore the importance of handling methods in experimental settings and suggest that while wheat and barley may enhance antioxidant defenses and tissue health, the influence on gut microbiota requires further investigation to optimize conditions that favor the growth of beneficial bacteria.

Overall, the combined findings indicate that Wheat and Barley-Derived Prebiotics, through their omega-3 content, enhance antioxidant defenses, promote colon health, and modulate gut microbiota, even within the context of a diet that includes components like soy and corn oil. This multifaceted impact underscores the importance of dietary composition in influencing oxidative stress, tissue integrity, and microbial balance in the gut.

CONCLUSION AND PERSPECTIVES

Conclusion

Prebiotics are highly effective substances that significantly improve the host's nutritional, physiological, and digestive functioning. This study investigated the prebiotic effects of wheat and barley on gut microbiota and health parameters in Wistar rats. To achieve this, we prepared a diet incorporating wheat and barley and administered it to Wistar albino rats for two weeks.

The biological activities were assessed in vivo by measuring malondialdehyde (MDA), catalase activity (CAT), and glutathione (GSH) levels, alongside histological examinations and bacterial analysis. Our findings indicated an effect on oxidative stress markers within this short experimental timeframe, evidenced by an effective antioxidant response to the prebiotic-rich diet, as demonstrated by increased CAT and GSH activity in conjunction with elevated MDA levels. Histological studies revealed a significant increase in colon thickness, while the presence of beneficial bacteria suggested a positive modulation of the gut microbiota. These results demonstrate that wheat and barley prebiotics can significantly enhance antioxidant activity and improve gut health even over a short-term period. The study underscores the potential health benefits of incorporating these prebiotics into the diet, advancing our understanding of their role in overall health. Although specific beneficial bacteria such as Bifidobacterium and Lactobacillus were not identified, the presence of other probiotic bacteria, such as Leuconostoc mesenteroides, suggests a favorable modulation of the gut environment. This modulation could support the antioxidant response by promoting the renewal of intestinal epithelial cells and increasing the production of tight junction proteins and mucin secretion. However, the detection of contaminants highlights the necessity for stringent handling practices to avoid environmental and inter-animal contamination. Additionally, the inclusion of mabroma, particularly its components like soy and corn oil, may have influenced the observed effects. While soy can potentially damage colon tissue at high concentrations, its effects were mitigated by the resistant starch in wheat and barley. Corn oil, known to increase oxidative damage, further explained the heightened oxidative stress markers. Despite these factors, the omega-3 fatty acids in wheat and barley likely contributed to the beneficial antioxidant activity, promoting mucosal integrity and cellular repair processes, thus enhancing colon thickness. Overall, wheat and barley prebiotics demonstrate a synergistic improvement in oxidative stress parameters and gut health. These findings highlight their potential to enhance antioxidant defenses, support mucosal integrity, and modulate the gut microbiota. The results underscore the importance of careful dietary formulation and handling practices in optimizing the health benefits of prebiotics.

Perspective

Future studies should explore the long-term effects of wheat and barley-derived prebiotics on gut microbiota composition and overall health, as well as their mechanisms of action. The use of advanced techniques is crucial for determining the molecular structure and structural characterization of wheat and barley from the El Oued region. Techniques such as High-Performance Liquid Chromatography (HPLC), Gas Chromatography-Mass Spectrometry (GC/MS), and Nuclear Magnetic Resonance (NMR) should be employed. Additionally, physicochemical and biochemical analyses, along with assessments of biological activities, are necessary.

Furthermore, it is recommended to measure other physiological parameters, such as glutathione peroxidase (GPX) and superoxide dismutase (SOD) levels, to gain a more comprehensive understanding of the antioxidant effects. For bacterial analysis, it is essential to identify the specific intestinal bacteria and evaluate how prebiotics affect the population of beneficial bacteria, such as Bifidobacterium and Lactobacillus, by examining the types and quantities of bacteria present in the gut using techniques like DNA sequencing, PCR, and culture methods. Understanding their impact on the gut environment by testing pH levels, mucosal integrity, and resistance to pathogenic bacteria is also critical.

By employing Multiphoton Microscopy (MPM), researchers can gain a comprehensive understanding of the histological alterations in the colon, providing valuable insights into the effects of prebiotics like wheat and barley on gut health. MPM allows for high-resolution, three-dimensional imaging of living tissues, enabling detailed observation of the colon's cellular and subcellular structures, deep tissue penetration, and reduced phototoxicity. This technique will help assess tissue architecture, cellular organization, and pathological changes, thereby enhancing our understanding of the role of prebiotics in maintaining gut health.

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ANNEX

Annex01. Histological sections of the large intestine at × 100 magnification

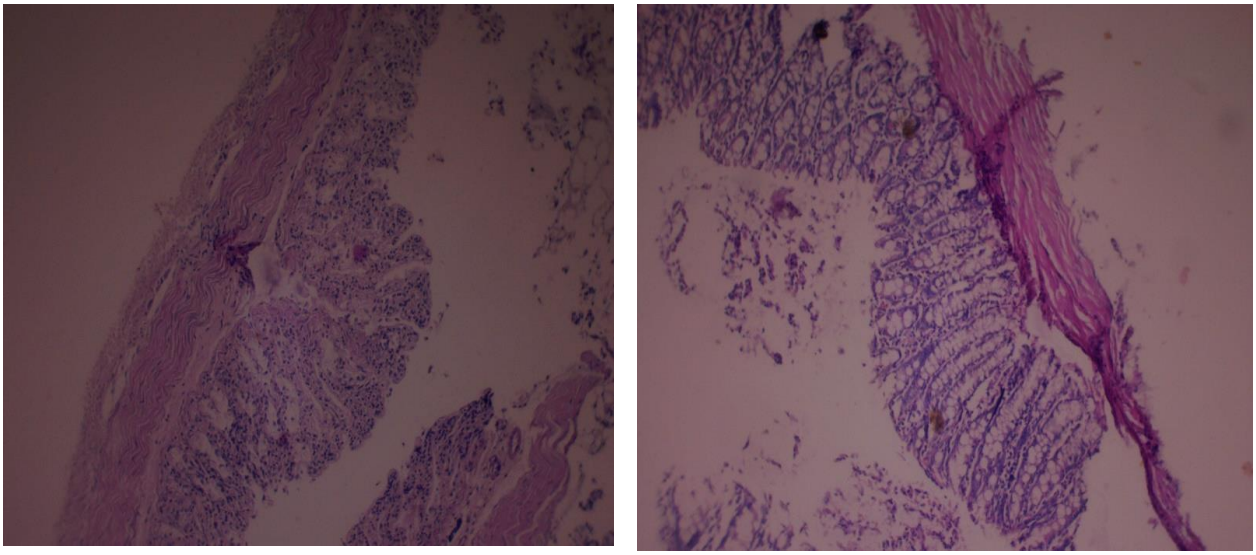

Photo01. Histological sections of the large intestine of normal and wheat

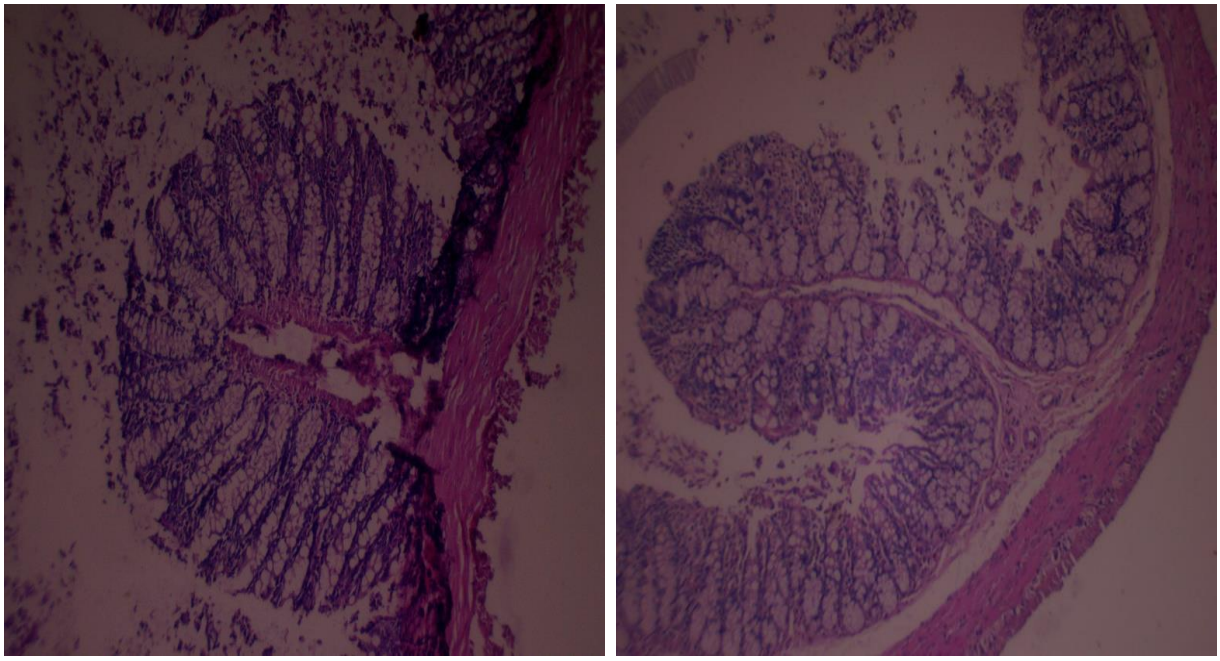

Photo02. Histological sections of the large intestine of barley and wheat+barley

Annex02. bacteria test

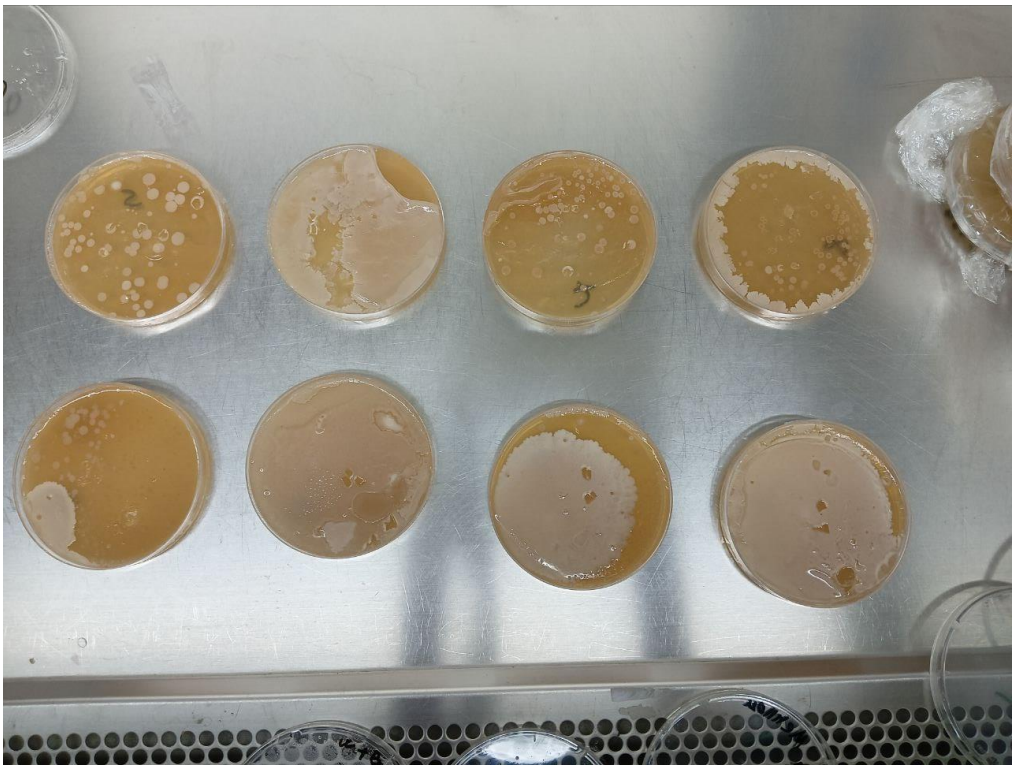

Photo03. the results of the bacteria test

Annex03. Sacrifice

Photo 04. Sacrifice of the rats