Saudi Journal of Biological Sciences 29 (2022) 103311

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

Genetic and epigenetic factors associated with depression: An updated overview

Dalal S. Alshaya

Department of Biology, College of Science, Princess Nourah bint Abdulrahman University, P.O. Box 84428, Riyadh 11671, Saudi Arabia

ARTICLE INFO

Article history:
Received 17 February 2022
Revised 28 March 2022
Accepted 15 May 2022
Available online 20 May 2022

Keywords:
Depression
Symptoms
Genetic factors
Epigenetic factors
Treatment

ABSTRACT

Depression is a complex psychiatric disturbance involving many environmental, genetic, and epigenetic factors. Until now, genetic, and non-genetic studies are still on the way to understanding the complex mechanism of this disease, and there are still many questions that have not yet been answered. Depression includes a large spectrum of heterogeneous symptoms correlated to the deficit of a range of psychological, cognitive, and emotional processes, and it affects various age groups. It is classified into several types according to the severity of symptoms, time of occurrence, and time. Following the World Health Organization (WHO), depression attacks near 350 million persons globally. Several factors overlap in causing depression, including genetic and epigenetic factors, environmental conditions, various stresses, lack of some nutrients to which people are exposed, and excessive stress and abuse in childhood. This study included conducting surveys on depression and new treatment trends based on epigenetic factors associated with the occurrence of the disease. Epigenetic factors provide a completely novel dimension to therapeutic approaches as most diseases are not monogenic, and it is likely that the environment has a significant contribution. Epigenetic inheritance is included in many mental and psychiatric disorders such as depression. In general, epigenetic modifications could be summarized in 3 major points: DNA methylation, histone modification, and non-mediated regulation of RNA (ncRNA). This study also describes some genes associated with one of the depressive disorders using bioinformatics tools and gene bank and had the genes: *SLC6A4, COMT, TPH2, FKBP5, MDD1, HTR2A,* and *MDD2*. As in this study, the awareness of Saudi society about depression and its genetic and non-genetic causes was estimated. The results showed that an encouraging percentage of more than half of the research sample possessed correct information about this disorder.

Contents

Abbreviations: SLC6A4, Solute Carrier Family 6 Member 4; COMT, Catechol-O-methyltransferase; TPH2, Tryptophan hydroxylase 2; FKBP5, FKBP Prolyl Isomerase 5; MDD1, Major Depressive Disorder 1; MDD2, Major Depressive Disorder 2; HTR2A, hydroxy tryptamine receptor 2A; NICE, National Institute for Health and Care Excellence; NIMH, National Institute of Mental Health; SAD, Seasonal Affective Disorder; MBCT, Mindfulness-based cognitive therapy.

E-mail address: dsalshaya@pnu.edu.sa
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2022.103311
1319-562X/

1. Introduction

Depressive is a major mental disorder that involves a large spectrum of heterogeneous symptoms related to the deficit of a group of psychological, cognitive, and emotional processes, and it is a common mental illness globally. According to the WHO, depression attacks about 350 million people worldwide. (Mill and Petronis, 2007). Depression is a disease with a broad and heterogeneous prognosis that attacks a huge proportion of the global population about 17–20% and is the fourth leading etiology of disability globally. Age distributions show that depression is prevalent in all life stages, affecting about 8% of men and 15% of women during their lifetime.

Depression is attributed to many known and unknown causes, where several elements overlap to cause depression, including genetic and epigenetic factors, environmental conditions, various stresses, deficiency in some nutrients to which people are exposed, as well as childhood abuse, and by the classic twin design, the researchers found that the effect of genetic and environmental impactions are involved in almost all psychological features (Franić et al., 2010), a small levels of certain hormones such as dopamine and serotonin have a significant impact on depression, and there are many clinical and molecular characters accompanied with depression that are hard to describe by classical genetic and environmental ways.

Also, the accumulation of free radicals in cells cause oxidative stress, which affect DNA and protein and may cause depression and finally death. The natural antioxidant may play vital role in mitigating the depression cause. The effective antioxidants include natural extracts (El-Saadony et al., 2020; El-Saadony et al., 2022; Abdel-Moneim et al., 2022), fiber enriched foods (Saad et al., 2015; Saad et al., 2021a), and bioactive peptides (Saad et al., 2021b; El-Saadony et al., 2021a, 2021b, 2021c).

Depression disrupts the typical adaptive and stress system and is distinguished by lack of interest and gladness in most daily works, low mood, and energy loss for at least two weeks. A huge range of psychological, biological, and social factors, which are not well recognized by current diagnostic approaches, still significantly affect the course of depression and its prognosis. Thus, it is essential to collect both personal and family histories of depression when making a diagnostic evaluation (Natale et al., 2022). The most common causes of depression are summarized in Fig. 1.

Not only does depression cause great psychological suffering, but it also negatively affects basic biological actions that control inflammatory process, clotting, metabolism, autonomic functions, endocrine control, sleep, and zest. The mortality rate in cases with major depression at any age regardless of suicide, smoking, or severe diseases. The World Health Organization has classified this disorder as the 4th leading etiology of disability globally (Andrey and Jaime, 2009; Kupfer et al., 2012; Gold et al., 2015).

This review included conducting surveys on depression and new treatment trends based on epigenetic factors associated with the occurrence of the disease. The epigenetic modifications could be summarized in 3 major points: DNA methylation, histone modification, and non-mediated regulation of RNA (ncRNA). This review article also described some genes associated with one of the depressive disorders using bioinformatics tools and gene bank and had the genes: SLC6A4, COMT, TPH2, FKBP5, MDD1, HTR2A, and MDD2. As in this review, the awareness of Saudi society about depression and its genetic and non-genetic causes was estimated.

2. Common signs of depression

According to Ettman et al., (2020) depression has many different signs including:

2.1. Emotional changes

Emotional changes as depressed person tends to feel sadness, irritability, sadness, guilt, anxiety, feeling helplessness or hopelessness, anger and/or Swings mood (Fig. 2).

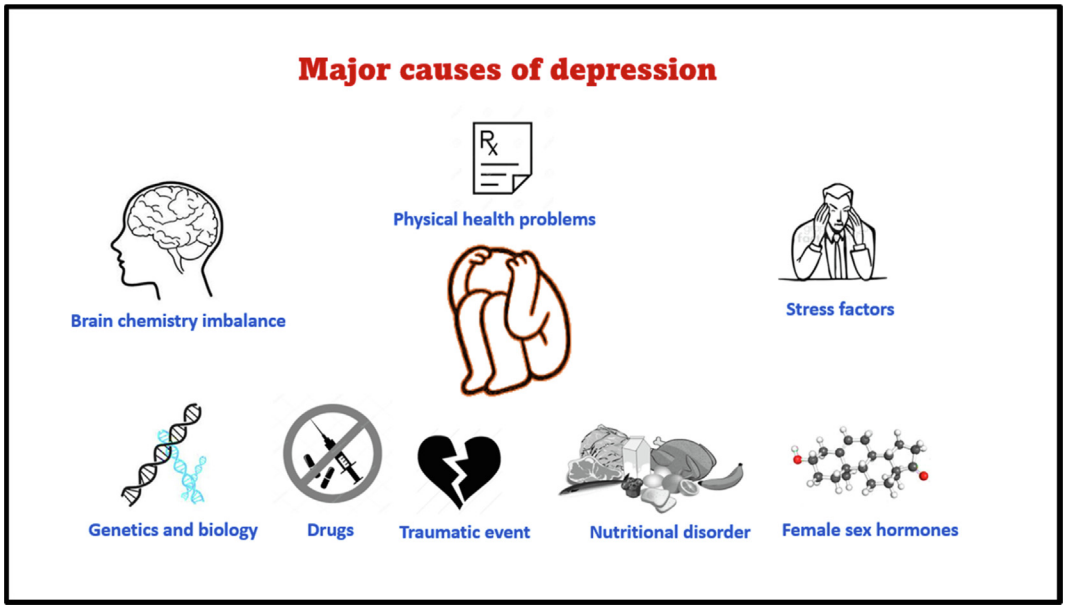

Fig. 1. Major causes of depression.

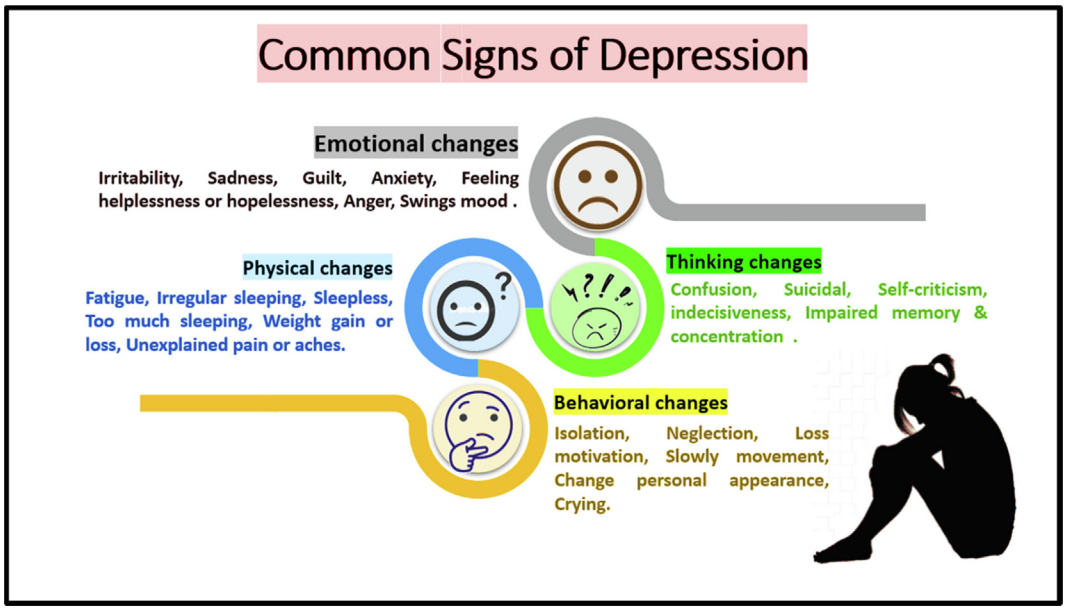

Fig. 2. Common signs of depression.

2.2. Thinking changes

Thinking changes as many negative thoughts dominate the depressed person's thinking as confusion, suicidal thinking, self-criticism, indecisiveness, impaired memory, and concentration (Fig. 2).

2.3. Behavioral changes

Behavioral changes as the depressed person tend to be isolated from the community around him, neglect their reasonability, loss motivation, slowly movement, change personal appearance, and tend to crying (Fig. 2).

2.4. Physical changes

Physical changes as depressed person usually suffered from continuous fatigue, irregular sleeping, sleepless or too much sleeping, weight gain or loss, suffered from unexplained pain or aches.

The term depression refers to a broad spectrum of overlapping mental disorders that are categorized via the (Diagnostic and Statistical Manual of Mental Disorders) according to the severity of depression and its associated features and are distributed into many types varying from bipolar I depression to major depressive disorder (Benazzi, 2006).

Description of Benazzi, (2006) has several subtypes of depression: bipolar I depression, bipolar II depression, mixed depression, agitated depression, atypical depression, melancholic depression,

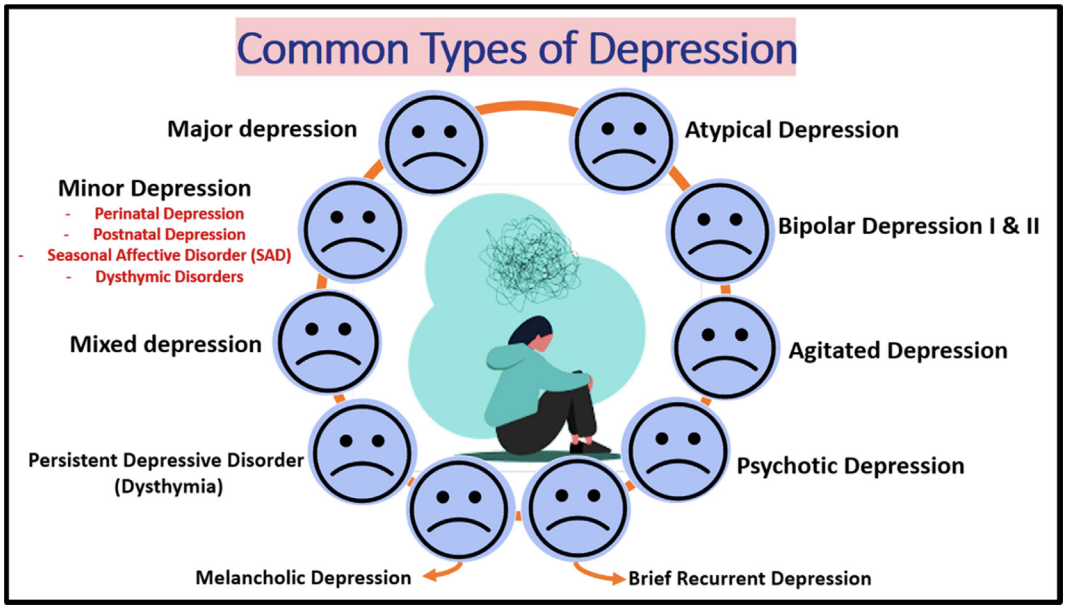

Fig. 3. Common types of depression.

brief recurrent depression, and minor depressive disorder including seasonal depression and dysthymic disorders (Fig. 3).

3. Depression classification

Based on National Institute of Mental Health (NIMH, 2011) the depression divided into following sections.

3.1. Major depression

Where the person suffers from signs of depression most of the day, almost repeatedly, for at least 2 weeks, and in a manner that interferes with the tendency to work, sleep, study, eat and enjoy life.

3.2. Persistent depressive disorder (dysthymia)

The patient suffers from signs of depression that extend for minimum about 2 years, and human with this type of depression may have episodes of major depression along with periods of mild signs.

3.3. Perinatal Depression

Females suffering from perinatal depression suffer from severe full-blown prepartum or postpartum depression.

3.4. Seasonal Affective Disorder (SAD)

It is a kind of depression that comes and goes with seasons and usually begins in late fall and early winter and goes away during spring and summer.

3.5. Psychotic depression

This kind of depression happened when human suffers from sharp depression in addition to some forms of psychosis, like disturbances in beliefs (delusions), hearing, or seeing disturbing things that others cannot hear or see (hallucinations).

Other models of depressive disorders involve dysthymia (diagnosed in children and adolescents) and premenstrual dysphoric disorder (www.nimh.nih.gov).

Decreased monoamine neurotransmission (serotonin and norepinephrine) and HPA axis dysregulation due to abnormalities in cerebral blood flow are among the main symptoms of depression. Antidepressant medications do early and effective treatment to maintain optimal brain function and lower the hazard of disease recurrence. Antidepressant medications increase monoamine neurotransmission so that they improve mood by regulating levels of serotonin and norepinephrine (Palazidou, 2012), and may provide other therapies that reduce neuroimmune activation and enhance anti-inflammatory pathways are alternative treatment options for subgroups of depressed individuals (Naismith et al., 2012). In general, the symptoms of depression of all kinds for the sufferer are in his lack of adaptation to the environment in which he lives with the loss of enthusiasm and energy in his daily activities, accompanied by noticeable changes in mood, and the treatment is through drug intervention or by helping the injured to engage in society (Mann and Currier, 2006).

Unlike most illness of the rest organ systems such as diabetes and tumors, for example, the diagnosis of depression is not based on objective diagnostic tests (serum chemistry, organ imaging, or biopsies) but a set of very variable signs. Accordingly, depression should not be viewed as a single disease but as a heterogeneous syndrome consisting of much illness with distinct etiologies and pathophysiology. The mixing of medicaments and psychotherapy (cognitive-behavioral) can synergize (Nestler et al., 2002).

Studies suggest that approximately 40–50% of the hazard of developing depression is genetic. However, the study for certain genes is frustrating, as no genetic anomalies have yet been identified with certainty. Depression is a complex phenomenon with many Genes, and any single gene may make a relatively little impact and thus would be hard to observe under experimental conditions. It is also available that variants in different genes may contribute to depression in each family, complicating the study for depression genes. Genes may directly or indirectly influence mood disorders, as susceptibility to depressive factors and stress is believed to have genetic underpinnings. Although there are many gaps in current knowledge, a model emerges in which

early life stressors can interact with genetic vulnerabilities, causing an elevated hazard of mood disorders (Nestler et al., 2002).

Since environmental factors appear to be particularly strong in depression, some focus has shifted to studies examining the reaction of genes with environment in recent years. For example, the serotonin genotype has been accompanied with grey matter loss in the hippocampus and frontal cortex of depressed cases subjected to early life stress. In addition, environmental experiences can alter gene action without altering DNA sequences (Palazidou, 2012) which are called epigenetic factors or epigenetic inheritance.

4. General features of depression

Depression is an abundant disease that could attack thoughts, mood, and physical health. It is described by low mood, loss of energy, sadness, restlessness, and failure to handle pleasure in life (Cui, 2015). It affects different age groups and is classified into several types according to the severity, time, and duration of symptoms (National Collaborating Center for Mental Health UK, 2010). It also affects females in a greater proportion. It constitutes a tremendous burden on health care providers around the world and on societies' economies as it affects the productivity of individuals and may lead to suicide or serious physical complications (Kupfer et al., 2012).

5. The depression genetics

It is difficult to identify the genes associated with depression because mental illness is subject to a polygenic influence and is related to interactions among genetic variants and environmental factors to many factors. Genetic and molecular studies continue to advance our knowledge of the biological basis of depressive disorder. However, the expanded to which findings from neurobiological research can help enhancement of clinical and functional outcomes for depressed persons remains uncertain (Kupfer et al., 2012).

Various methodological methods such as candidate gene analysis, genome-wide association analysis, and genome-wide sequencing have been utilized. Many associations between genes and different phenotypes of depression have been identified. Still, these associations have not been confirmed in replication research in most cases. A little count is only one of the genes is associated with the hazard of existing a type of depression (Shadrina et al., 2018). Although genetics have a role in the cause of depression, identical twin studies showed large variation rates, suggesting non-genetic techniques as well. For example, persistent stress increases the hazard of depression, and environmental stressors also lead to persistent changes in gene expression (Gene Expr.) levels within the brain, leading to decreased neuroplasticity in areas related to disease development. (Uchida et al., 2018).

Opportunities to study changes in the state of depression are restricted by the nature of the disorder and the require analyzing cranial cells, which is only available after death. Thus, research should be complemented by using various animal models of depression, which would provide a possible way to assess the correlation of genetic, epigenetic, and environmental effects to the occurrence of various forms of depression and aid existence of the treatment methods. The existence of DNA microchip technology made it available to perform genome-wide association studies (GWASs) to search for hazard factors for the onset of depression. However, GWASs that use large sample sets, involving thousands of cases with various forms of depression, failed to identify any particular locus accountable for the occurrence of the disease. This failure to determine genetic associations and underlying mechanisms indicates that depression is a heterogeneous and multifactorial psychiatric disorder, which suggests that predisposing factors to depression is controlled by the function of several genes and their reaction with each other and various environmental factors. Some studies have reported that genetic differences in mitochondrial DNA may be accompanied with depression (Gibney and Nolan, 2010; Shadrina, et al., 2018).

6. Definition of epigenetics

Epigenetics (epigenetics) is the science that studies the external change of DNA without a change at the level of the nucleotide sequences in the DNA, which affects the function of the gene, its behavior, and its production of protein, and this change occurs due to the addition of some molecules and chemical compounds of DNA molecules, these chemical compounds are called the epigenetic genome, where the DNA is wrapped around the histone octagons to form the chromatin unit.

Tgene activity is reflected in the structure around the chromatin: the genes inside the relatively differentiated genetic nuclei are actively transcribed; In contrast, genes in tightly coiled nucleosomes are silenced, nucleosome spacing is regulated by highly complex mechanisms, including post-translational modification of histones and DNA and the recruitment of huge count of chromatin controlling proteins that react with these changes. DNA, but only attached to it, and these epigenetic changes continue through cell division and maybe It is passed down from parents to children. (Nestler, 2014).

7. Epigenetic factors

The most important factors that lead to epigenetic changes are the style and pattern of feeding, exposure to various environmental pollutants, bad habits such as smoking, use of certain medications, exposure to certain types of diseases, especially during childhood (Baccarelli and Bollati, 2009).

8. Depression and epigenetic factors

Studies and statistics, as well as laboratory experiments on mice and experimental animals, have proven that environmental or internal physiological external factors such as continuous psychological stress, harsh environmental conditions, or psychological trauma interact with the individuals' genetic total and lead to many changes at the epigenetic level, where this could be available via epigenetic techniques that resulting in variations in Gene Expr. with transgenerational abilities that do not include a variation in the DNA sequence, by increasing or decreasing rates of DNA methylation, as well as altering the formation of histones around the DNA, which affects the expression of some proteins, by increasing or decreasing, as the levels of hormones that contribute to depressive episodes vary, basing on the conditions and factors of the environment, the nutrition, and physical activity (Fig. 4).

Some people's behavior and inclinations to depression, addiction, or suicide, through epigenetic inheritance, which can be passed down through generations, and scientists have linked the above genes. Many other psychiatric diseases, such as Alzheimer's, schizophrenia and epilepsy, and these studies are promising in discovering new drugs to treat or prevent these diseases (Saavedra et al., 2016; Pena and Nestler, 2018). Epigenetic events change chromatin composition and therefore modulate the Gene Expr. that have a role in neuroplasticity, behavioral reaction to stress, depressive behaviors, and react to antidepressants.

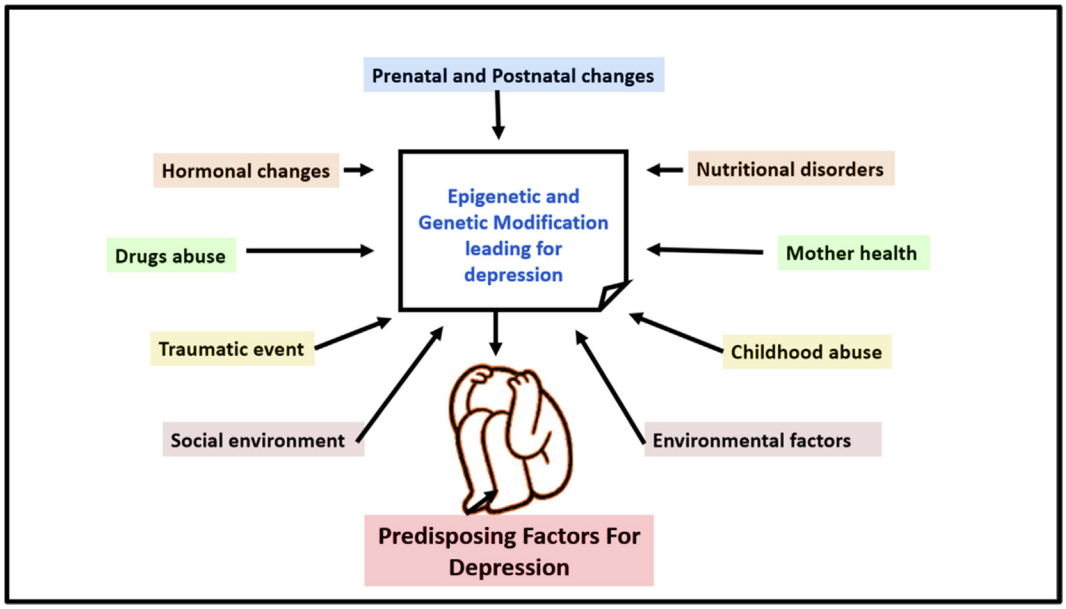

Fig. 4. Predisposing factors for depression.

9. Mechanisms of epigenetic changes

Epigenetic changes occur by several mechanisms, including methylation (adding the methyl molecule CH3), one of the most common epigenetic changes. The methyl molecule, consisting of 3 hydrogen atoms attached to a carbon atom, is connected to parts of DNA molecules, leading to this gene's disruption. It stops working and stops producing the protein that carries its code. As a result, several errors may occur in adding or not adding these chemical molecules, which are responsible for the work and stop of many genes, which leads to many errors and diseases such as cancer and mental illness, which may be passed on through generations (Natale et al., 2022).

10. Histone change (change at the level of histones)

Histones are proteins that wrap around DNA. They are the first nuclei to form chromatin, which unites DNA to create the chromosome. The change that occurs to these proteins helps to read and translate more genes, which allows for the emergence and expression of more proteins, which is evident in the body's cells. Genes are expressed in these cells, while reading these genes stop in another type of cell (Natale et al., 2022).

10.1. Re-forming chromatin

Through many enzymes, allows more DNA genes to express themselves, appearing after reading them, or disappearing, and this happens by adding a methyl molecule, demethylating a molecule, or adding an acetylcholine molecule, or removing the acetylcholine molecule from the chromatin chain. Non-coding RNA RNA molecules have several types (miRNA- siRNA-piRNA IncRNA), and it plays their role in regulating the reading process and expression of different genes. It is involved in epigenetic change processes, and studies have proven its involvement in many causes of Diseases such as cancer (Local and Ventura, 2018).

10.2. Behavioral epigenetics

Behavioral epigenetics studies the relationship and effect of nature and various environmental impacts on genes and the appearance of these genes. For example, identical twins have the same DNA content, but they differ in behaviors, diseases, mental and intellectual abilities, and even general appearance. Scientists have called this science, which is concerned with studying the effect of different environments and upbringing conditions on the appearance of genes and brain behavior, the name behavioral epigenetics (Natale et al., 2022).

Scientists believe that the impact of various environmental factors on genes begins very early since the human being is a fetus in his mother's womb, the environment surrounding the mother, her food habits, different lifestyles, her exposure to toxic substances, exercise, hormones, or smoking, etc., affect this. In addition, the fetus, its mind and its genes and their expression in the future, and scientists and recent research in epigenetics suggest that these genes have a significant role in many diseases, such as cancer, autism, schizophrenia, obesity, diabetes, mental retardation, some neurological disorders, and even societal behavior, such as addiction: delinquency, suicide (Natale et al. 2022).

One of the most critical traits that super-genes affect is the ability to learn and remember, where scientists recently found a strong relationship between changing histones, adding a methyl group to DNA molecules, and learning and remembering. It is also believed that there is a significant relationship between adding a methyl group to DNA and the chances of occurrence of cancers. Also, the behavior of the fathers and mothers has a significant impact on the epigenetic genes of the children, and this was shown in the experimental mice, as the young mice are affected by the mother's behavior and the extent of her care for the young mice. The mother of some toxic substances, which may affect DNA methylation, affects the epigenetics of fetuses and children. In an experiment conducted on experimental mice, in which the male and female were exposed to alcohol immediately before the mating process, this led to the birth of small, weak mice with a hostile behavior greater than Mice whose parents were not exposed to the same conditions, imprinting also dramatically affects the epigenetic or epigenetic inheritance, where the characteristics of one parent prevail over the other, an example of which is the mule (Powledge, 2011).

11. An epigenetic perspective

Epigenetics indicates to fixed changes in Gene Expr. that take place across structure-variable chromatin without modifying the

DNA sequence. Gene Expr. that contributes to depressive episodes and the result of this hypothesis is that like stress-stimulated epigenetic modifications also happened early in life and aid to detect persons lifelong vulnerability or resistance to subsequent stressors. However, there are also two ways genetic techniques can impact depression. The first includes random events during growth, and the other relates to true genetic inheritance across many generations (Nestler et al., 2002).

Gene action can be changed by more than just alterations in the genome sequence. Many epigenetic mechanisms, involving DNA methylation and histone modifications, can alter genome action under external effect, and the possible evidence provides the concept that epigenetics holds great potential to advance our knowledge about the molecular techniques of environmental toxins, also to predict health-related hazards because of the environmental exposure status and allergies—the person. An increased understanding awareness of the mechanisms of epigenetic inheritance can lead to layers of disease risk assessment for targeted intervention and targeted therapies.

A large range of diseases, behaviors and other health indicators already have some level of evidence linking them to epigenetic mechanisms, involving tumors of nearly all types, cognitive dysfunction, respiratory diseases, cardiac, reproductive, autoimmune, and neurological diseases. Known or suspected factors behind genetic mechanisms involve several factors, as heavy metals, pesticides, diesel exhaust, tobacco smoke, polycyclic aromatic hydrocarbons, hormones, radioactivity, pathogens, stressors, emotional trauma, viral infections such as Bornavirus, and even random processes during Brain development. However, stress itself is not enough to etiology depression. Most people do not become depressed post severe stressful experiences, while many who become depressed do so post stresses that are mild for most people. Conversely, extreme stress experienced during combat does not usually lead to depression. Instead, it reveals to post-traumatic stress disorder (PTSD), which is different from depression, and this confirms that depression in most persons is because of the interactions among genetic predisposition and some environmental conditions (Bollati and Baccarelli, 2010).

A comprehensive survey of all available scientific databases was conducted to identify studies related to depression and its association with genetic, epigenetic, or environmental factors during the years 2003–2020, as the capability to test epigenetic processes in the encephalon became readily possible exceed the past twenty years, which resulting in an expansion in study and interest in neurobiological and behavioral epigenetics. As a result, it has become essential for everyone—especially researchers—to know that epigenetic processes, like alterations in DNA methylation and histone modification, constitute a biochemical report of environmental influences and how molecular alterations in the encephalon can regulate behavior (Isles. 2015).

Scientists attempted to explain disorders solely by genetic or environmental factors for a long time. However, research has increased in epigenetics, chromatin action in the brain, and behavior over the past 2 decades. However, epigenetics as a biological concept preceded the discovery of DNA in the 1950s as a fundamental mode of inheritance for more than a decade, particularly in complex disorders like behavior, memory, tumors, autoimmune diseases, addiction, also neurological and psychiatric disorders (Moosavi and Ardekani, 2016; Isles, 2018).

The thought of epigenetics was 1st supported in the 1940s by Conrad Waddington (1942), an embryologist interested in the techniques of cell differentiation, who noted that since all cells carry the same genetic information, there should be a layer level Another piece of knowledge in addition to genetic information that allows the whole cell to become specified and remain specified in the later stages of development (Isles, 2018).

In general, epigenetics refers to the science concerned with studying inherited changes in the phenotype that do not happen because of the alterations in the DNA sequence. In another words, epigenetics is the science that studies particularly external and environmental factors that activate or inactivate the action of genes and impact how the cell reads genes (Moore, 2015). Saavedra et al. (2016) referred to epigenetics as changes that occur in Gene Expr. that are not because of the differences in the DNA sequence. These alterations can be heritable and environmentally changeable, and epigenetics can explain various factors situations. It is difficult to describe through traditional genetics. Epigenetic regulation is fundamental to many cellular mechanisms, involving Gene Expr., DNA-protein interactions, transposable element repression, cellular differentiation, embryogenesis, X chromosome inhibition, etc. (Soga et al., 2021).

Epigenome generally includes all epigenetic modifications like DNA methylation and histone modifications, as well as non-coding RNAs at any time. This trait can be helpful in complex traits and challenging disorders like memory function, behaviors, psychological injury, addiction, cancer, and other disorders that cannot be explained solely by genetic factors or the environment. In addition, genetic modifications can be reversible, making the genome flexible in response to environmental changes such as nutrition, stress, toxicity, exercise, and medications. For example, acetylation of histone subunits either enhances gene transcription or represses genes (Moosavi and Ardekani, 2016).

The genome of eukaryotes is organized by wrapping DNA around octahedrons to form the basic units of chromatin, nucleosomes, which are organized and compacted into higher-order structures—genes contained in tightly packed nucleosomes (Nestler, 2014). Depression is a complex psychiatric disorder involving several environmental, genetic, and epigenetic factors. About 30–40% of all types of depression are genetic (Edvardsen et al., 2009). Until now, genetic, and non-genetic studies are still on the way to understanding the complex mechanism of this disease, and there are still many questions that have not yet been answered.

Genome-wide studies (GWAS) to identify factors accompanied with depression at the genome level have contributed to answering some of the existing questions about the disease (Chang et al., 2018). Recently, some complex disorders to epigenetics have emerged, which are permanent alterations in Gene Expr. that are not a result of a change in the sequences of the nucleotide arrangement of the genetic material and can be passed on to future generations (Natale et al. 2022). Epigenetic mechanisms, like DNA methylation, histone acetylation and microRNA dysregulation, may play a role in depression (Dalton et al., 2014).

Several studies have suggested that depressive symptoms are caused by decreased levels of the neurotransmitter's serotonin and dopamine (Phillips, 2017), which are under the control of genes: SLC6A4 Serotonin transporter gene TPH2 transporter gene, Tryptophan hydroxylase and COMT gene. Where it was observed that most people with depression have a lower-than-average level of these hormones, which led scientists to invent a new generation of medicaments that raise the level of serotonin in the encephalon, and neurons in the brain secrete the hormone dopamine within many distinct pathways, one of which plays It plays a pivotal role in neuromodulation, which makes changing its levels cause neurological disorders (Zahavi et al., 2016).

On the relationship of disease to both genetics and the environment, via the classic twin design, the studies discussed the action of genetic and environmental effects in nearly all psychological traits. In the children, surveys acquired from teachers, beside parental ratings, are an essential source of knowledge on childhood growth and psychopathology, and genetic and environmental impacts may be age related. For example, anxiety or depression

at age five is like that at age 10, and demonstrations of progression-related alterations in anxiety and depression, in general, have revealed that these disturbances are reasonably fixed during childhood.

However, several children who primary display relatively large levels of anxiety or depression develop normally, while some other children, who show primary regular development, develop anxiety or depression at a later age. The variations generally indicate an effect of shared environment on childhood anxiety and depression that fades as children enter their teenage years 17–21. In adulthood, the impact of the familiar environment disappears, and the relative impact of genetic effects elevates. Consequently, the heritability of these traits elevates with age (Franić et al., 2010).

Environmental factors such as heat and oxidative stresses adversely affect genetic alterations in a specific genetic locus that aid shape neuronal plasticity and action. Thus, behavior and some of these alterations can be very fixed and persist throughout life. All living things constantly face stressors and differences in their environment that impact their balance. Stress reacts to these external challenges and includes changes in the CNS and various peripheral systems that target to restore primary balance. These changes impact the CNS directly. Learning, memory, vigilance, agitation, and anxiety enhance adaptive behavioral responses to subsequent stressors. One of the ways to ease these stressors is by adding some natural compounds to the food of these people such as phytogenic bioactive compounds (Abd El-Hack et al, 2021a, 2021b), prebiotics (Yaqoob et al, 2021; Abd El-Hack et al., 2021c), probiotics (Alagawany et al., 2021; El-Saadony et al., 2021d), and natural pigments (Abdelnour et al, 2020a, 2020b).

The inability to control and end these stress responses can lead to many forms of dysregulation, which profoundly affect neuroendocrine systems, involving immune, metabolic, and reproductive responses. Stressful experiences have been shown to elevate the incidence of many health problems, involving coronary artery disease, chronic lung infections, and some types of cancer. Stress can negatively impact behavioral adaptations and predispose some persons to depression or anxiety-related disorders. However, substantial interindividual variability in susceptibility to stress may be attributed to genetic factors. Most resilient individuals could keep regular physiological and psychological functions despite being exposed to appalling stress (Soga et al., 2021).

Animal models of stress-related disorders help reveal specific chromatin alterations that keep fixed patterns of Gene Expr. and thus influence the level of neuroplasticity accompanied with these disorders; research in mice have revealed that epigenetic factors can affect maternal behavior and that this impact can be passed on from one generation to the next by acting on the young brain alone, without changing the germ cells. When the young are born, the genes included in controlling the animals' responses to stress are methylated differently, enhancing sensitivity to stress (Abdelnour et al., 2020a; Reda et al., 2021a, 2021b). As the young ones mature, they will become more vigilant parents. Whereas if the young are raised by a mother who shows small levels of flexibility, their genes will have methylation marks. They then grow up to be more responsive to stress and, in turn, show smaller levels of care towards their young (Soga et al., 2021).

Concerning epigenetic factors and depressive disorders, it has been confirmed that epigenetic genetics has an effective role in developing different mental and psychological disorders as depression. In general, epigenetic modifications can be summarized in 3 general points: DNA methylation, histone modification, and non-mediated regulation of RNA (ncRNA) is a crucial epigenetic regulation in the pathophysiological process of depression (Vialou et al., 2013).

According to Kuehner et al., (2019), studies of epigenetic factors provide an entirely new dimension to treatments due to most of these diseases are not monogenic, and the environment is likely to have a critical contribution, as epigenetic genetics is severely impacted by environmental factors like nutrition, chemical pollutants, traumatic early life experiences, temperature differences and exercise, but how they influence brain growth is not well understood. Significantly, the influence of the environment on epigenetics is not limited to growth post birth but can also affected by intrauterine growth. The stresses of early life that cause long-term genetic alterations can be due to a congenital genetic 'predisposition'. Like the immune system, once exposed to certain environmental rays and a change in genetic status, that gene is now in an "initial response" state and will have a faster reaction if that environmental stress is exposed again; This concept of epigenetic memory in react to environmental stimuli could act as a means of identifying persons who are prone to developing neuropsychiatric diseases (Soga et al., 2021).

Guo et al. (2014) noticed that, in addition to direct DNA modification, epigenetic control could also be performed by alterations to the three-dimensional structure and histone proteins associated with DNA, as the DNA within the nucleus is not stripped, as it is wrapped around histone octaves to form nucleosomes that are formed into ordered chromatin composition. Gradually, chromatin states are generally classified into chromatin (open) and chromatin (closed) and are determined by several possible modifications such as acetylation, methylation, and phosphorylation processes (Natale et al., 2022).

NR3C1 and depression. Increasing evidence indicates that epigenetic modification is critical in the biological mechanisms of depression, and DNA methylation has been considered a potential link among the environment and depression. In the study of Chen et al., (2017), the relationship among DNA methylation of seven genes: (FKBP5), (MAO-A), (OXTR), (BDNF), (5-HTR), (SLC6A4), and (SLC6A4) was reviewed. Most of the results revealed that the methylation levels of the genes: BDNF and NR3C1 were associated with depression, while the association of SLC6A4 and depression were inconsistent. The study notes that longitudinal studies in animal models and patients with depression are urgently recommended to learn more about the role of DNA methylation in depression (Soga et al., 2021).

The growth of DNA microchip technology has made it available to perform genome-wide association studies (GWASs) to look for factors that increase the chance of developing a depressive disorder. These studies did not unequivocally identify the mechanisms of Biological Underlying Pathogenesis. Large samples, involving thousands of cases with various forms of depression and tens of thousands of cases in the following analysis, but those studies unable to determine any particular locus responsible for predisposition to depression.

This inability to identify genetic associations and underlying mechanisms indicates that depression is a heterogeneous and multifactorial psychiatric disorder. Susceptibility to infection is likely decided by the coordinated action of several genes and their interaction with each other and diverse environmental events. It is also possible that each gene makes a little relation to the pathogenesis of the illness (Soga et al., 2021).

Despite the encouraging results obtained by scientists so far, one of the significant challenges in studying psychiatric and neurological diseases, according to Kuehner et al., (2019) is the limitations of the available model systems, as models of mouse and human encephalon after death have been highly relied upon to support insight into. In pathology, neurological and psychiatric diseases. However, both choices have restrictions. Although rat and human brains are same at the levels of genetic, structural, and general circuits, significant variations limit them as models for human disease because of the complex dysfunction in behavior and thought in rat brains. For example, human brains are more devel-

oped because the granular prefrontal cortex contains parts of cognition absent in mouse brains.

Furthermore, human brain specimens are available after death and therefore can never summarize the genetic landscape of the living brain. Moreover, a postmortem (PM) is only a snapshot in the disease timeline, and this snapshot is usually biased towards the state of death. Therefore, PM human brains unable to support data on disorder start and progression along time (Soga et al., 2021).

12. The control of depression

Depressive symptoms can be relieved with medication and brief psychotherapy (cognitive-behavioral and interpersonal therapy). Additionally, combination therapy has been linked to greater rates of depressed symptom improvement, improved quality of life, and better treatment adherence. CBT's effectiveness in preventing relapse is also supported by research (Horowitz and Taylor, 2019). Also, patients who do not respond well to drugs or are suicidal may benefit from electroconvulsive therapy (Salik and Marwaha, 2021). Standard tools for depression control are summarized in Fig. 5.

12.1. Most common medicaments for the treatment of depression

Many drugs are available for the treatment of depression with different ways of action as: Typical antidepressants, Selective serotonin reuptake inactivators, serotonin/norepinephrine reuptake inhibitors, Serotonin-Dopamine Activity Modulators, Monoamine oxidase inhibitors, and Tricyclic antidepressants (Bennabi et al., 2019; Gałecki et al., 2022).

12.2. Electroconvulsive therapy (ECT)

ECT is a very successful depression treatment. The onset of action may be faster than with medications, with benefits frequently visible within 7 days of starting treatment. Patients who do not react to medication therapy, are psychotic, or are suicidal or harmful to themselves should consider an ECT course (typically up to 12 sessions). As a result, the following are some of the indications for using ECT: a fast antidepressant reaction is required as drug therapy has failed, patient inclination, suicide risk is predicted, ECT has a strong track record in the past, the hazard of medical therapy. Although developments in brief anesthesia and neuromuscular paralysis have progressed ECT's safety and tolerability, treatment still has several hazards, including those related to general anesthesia, postictal disorientation, and, in rare cases, short-term memory problems (Bennabi et al., 2019; Gałecki et al., 2022).

12.2.1. Psychotherapy

Evidence-based psychotherapies like Cognitive Behavior Therapy and Interpersonal Therapy have been demonstrated to be potent in depression treatment (Gałecki et al., 2022).

12.2.2. Cognitive-behavioral therapy (CBT)

CBT is a systematic and didactic type of treatment that focuses on assisting people in identifying and altering hazard thinking and behavior styles (16–20 sessions). It is predicated on the idea that depressed people display the "cognitive triad" of sadness, which involves a negative perception of themselves, the world, and the future. Patients with depression have cognitive distortions that aid in the maintenance of their negative views. CBT for depression usually consists of behavioral methods (such as activity scheduling) and cognitive restructuring to shift automatic negative thinking and address maladaptive schemas (Gałecki et al., 2022).

Mindfulness-based cognitive therapy (MBCT) aims to decrease relapse in people who have had successful treatment for recurrent major depressive disorder. Mindfulness training is the main therapeutic component. The MBCT program focuses on ruminative mental processes as a relapse hazard factor. MBCT appears to help reduce the likelihood of relapse in cases with repeated depression, particularly in those with the most severe remaining signs (Caraci et al., 2018; Gałecki et al., 2022).

There is evidence that CBT can be used with people of various ages. It's especially useful for senior individuals, who are more likely to have issues or negative effects from drugs (Zhdanava et al., 2021; Gałecki et al., 2022). It is also thought to be effective in the avoidance of recurrence.

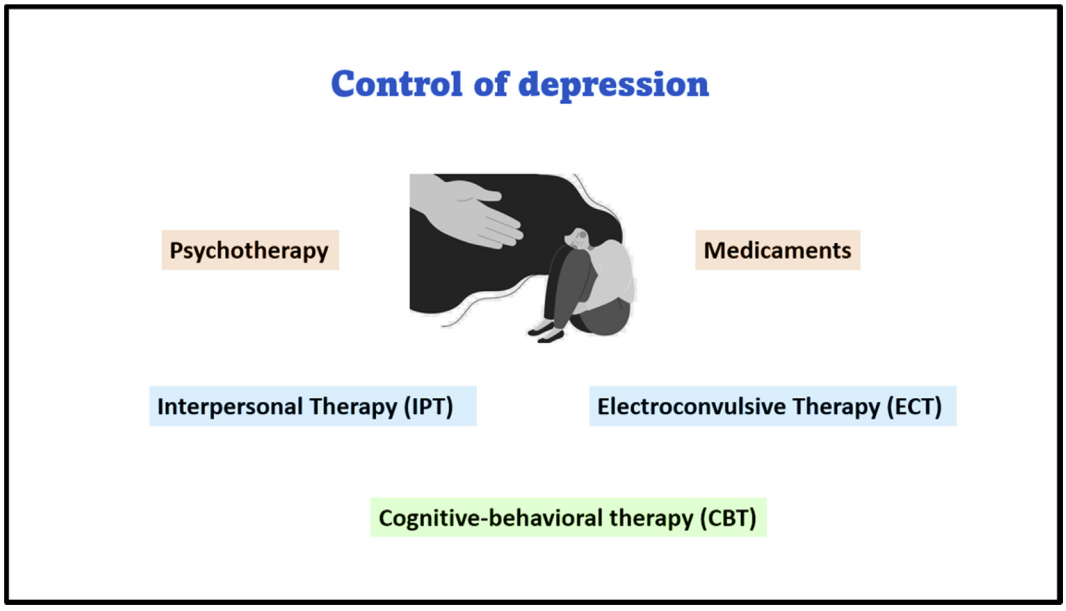

Fig. 5. Major tools for control of depression.

12.2.3. Interpersonal therapy (IPT)

Interpersonal therapy (IPT) is a time-limited treatment for major depressive illness (usually 16 sessions). IPT is based on attachment theory and emphasizes the importance of interpersonal connections, concentrating on contemporary interpersonal issues. Grief, interpersonal conflicts, role shifts, and interpersonal deficiencies are all focus topics (Gałecki et al., 2022).

12.2.4. Differential diagnosis of the depression

Depression should be differentiated from the following conditions: somatic symptom illness, anemia, schizophrenia, adjustment disorders, schizoaffective disorders, dissociative disorders, hypopituitarism, anxiety disorders, hypoglycemia, and chronic fatigue syndrome (Zhdanava et al., 2021).

12.3. Several points were also emphasized, including

1. Exposure to environmental influences in utero or early life produces impacts that could be inherited across generations and are associated with genetic or epigenetic changes.
2. Major diseases with late phenotypes include genome-environment interactions. Increasing understanding of epigenetic disease pathogenesis can lead to disease risk assessment for targeted intervention and targeted therapies.
3. Depression is a polygenic disease, so genetic contributions are due to different genes, each with relatively little impact.
4. New imaging and treatment technologies are constantly being developed, and new treatments for acute episodes of major depression or prevention of recurrent episodes hold great promise. There are also many other molecularly targeted agents currently under investigation.
5. The growing knowledge about the mechanism of depression provides for the existence of drugs to target the disorder more effectively: Antidepressant drugs improve serotonin and norepinephrine levels, restore neuronal growth and activation, after identifying and identifying the epigenetic change, and identifying the methodology and mechanisms of epigenetic changes, which cause some Diseases of stress, anxiety and depression, and this has become a promising way to make medicines through which these biochemical reactions are controlled.
6. It was emphasized that the difference in Gene Expr. plays a dominant role in individual differences: Studies and statistics have proven that exposure to continuous psychological stress, harsh environmental conditions, or psychological trauma leads to many changes at the epigenetic level, which leads to an increase or Decreased rates of addition of methyl molecule to DNA.

13. Conclusion

Through the previous review, we conclude that the genes that are related to depression are divided into Genes directly affect the neurotransmitters of hormones related to depression, for example, the SLC6A4 Serotonin transporter gene on chromosome 17 and the TPH2 transporter gene Tryptophan Hydroxylase on chromosome 12, as well as the COMT gene on chromosome 22. (The description of all genes is explained in the next point from RESULTS: Results of genetic characterization of genes associated with depressive disorders). Genes that have an indirect effect on the occurrence of depression, which are more than 100 different genetic loci that have been identified through whole-genome association studies (GWAS), where this type of study examines the entire genome, rather than identifying and studying specific genes or genetic regions, which help identify variables associated with a disease or identifying genetic factors affecting a trait. Epigenetic factors studies have shown their close relationship to the occurrence of depression.

14. Recommendations

1. Spreading awareness about the causes of depression in various media outlets and holding forums and symposiums about them to give the subject its right to media and educate the community about the importance of epigenetic factors and their impact on the occurrence of mental illness disorders.
2. Establish psychological support centers within the primary health and family medicine centers in Saudi Arabia.
3. Providing the units and capabilities of teachers and sufficient human cadres specialized in epigenetics in research centers around the Kingdom.
4. Care to conduct more studies and research on the lifestyle of individuals and its role in increasing the risk of diseases with an everyday genetic and environmental basis.

Acknowledgment

The author extend her appreciation to the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia, for supporting this research work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abd El-Hack, M.E., Alaidaroos, B.A., Farsi, R.M., Abou-Kassem, D.E., El-Saadony, M.T., Saad, A.M., Shafi, M.E., Albaqami, N.M., Taha, A.E., Ashour, E.A., 2021b. Impacts of supplementing broiler diets with biological curcumin, zinc nanoparticles and *Bacillus licheniformis* on growth, carcass traits, blood indices, meat quality and cecal microbial load. Animals 11 (7), 1878.

Abd El-Hack, M.E., El-Saadony, M.T., Shafi, M.E., Alshahrani, O.A., Saghir, S.A., Al-Wajeeh, A.S., Abdel-Moneim, A.M.E., 2021c. Prebiotics can restrict Salmonella populations in poultry: a review. Anim. Biotechnol., 1–10

Abd El-Hack, M.E., El-Saadony, M.T., Swelum, A.A., Arif, M., Abo Ghanima, M.M., Shukry, M., Noreldin, A., Taha, A.E., El-Tarabily, K.A., 2021a. Curcumin, the active substance of turmeric: its effects on health and ways to improve its bioavailability. J. Sci. Food Agric. 101 (14), 5747–5762.

Abdel-Moneim, A.M.E., El-Saadony, M.T., Shehata, A.M., Saad, A.M., Aldhumri, S.A., Ouda, S.M., Mesalam, N.M., 2022. Antioxidant and antimicrobial activities of Spirulina platensis extracts and biogenic selenium nanoparticles against selected pathogenic bacteria and fungi. Saudi J. Biol. Sci. 29 (2), 1197–1209.

Abdelnour, S.A., El-Saadony, M.T., Saghir, S.A.M., Abd El-Hack, M.E., Al-shargi, O.Y.A., Al-Gabri, N., Salama, A., 2020a. Mitigating negative impacts of heat stress in growing rabbits via dietary prodigiosin supplementation. Livest. Sci. 240, 104220.

Abdelnour, S.A., Swelum, A.A., Salama, A., Al-Ghadi, M.Q., Qattan, S.Y.A., Abd El-Hack, M.E., Khafaga, A.F., Alhimaidi, A.R., Almutairi, B.O., Ammari, A.A., El-Saadony, M.T., 2020b. The beneficial impacts of dietary phycocyanin supplementation on growing rabbits under high ambient temperature. Ital. J. Anim. Sci. 19 (1), 1046–1056.

Alagawany, M., Madkour, M., El-Saadony, M.T., Reda, F.M., 2021. *Paenibacillus polymyxa* (LM31) as a new feed additive: Antioxidant and antimicrobial activity and its effects on growth, blood biochemistry, and intestinal bacterial populations of growing Japanese quail. Anim. Feed Sci. Technol. 276, 114920.

Andrey, S.C., Jaime, F.T., 2009. Neurobiología de la depresión. Revista Mexicana de Neurociencia 10 (6), 462–478.

Baccarelli, A., Bollati, V., 2009. Epigenetics and environmental chemicals. Curr. Opin. Pediatr. 21 (2), 243–251.

Benazzi, F., 2006. Various forms of depression. Dialogues Clin. Neurosci. 8 (2), 151–161.

Bennabi, D., Charpeaud, T., Yrondi, A., Genty, J.-B., Destouches, S., Lancrenon, S., Alaïli, N., Bellivier, F., Bougerol, T., Camus, V., Dorey, J.-M., Doumy, O., Haesebaert, F., Holtzmann, J., Lançon, C., Lefebvre, M., Moliere, F., Nieto, I., Rabu, C., Richieri, R., Schmitt, L., Stephan, F., Vaiva, G., Walter, M., Leboyer, M., El-Hage, W., Llorca, P.-M., Courtet, P., Aouizerate, B., Haffen, E., 2019. Clinical guidelines for the management of treatment-resistant depression: French

recommendations from experts, the French Association for Biological Psychiatry and Neuropsychopharmacology and the fondation Fonda Mental. BMC Psychiatry 19 (1).
Bollati, V., Baccarelli, A., 2010. Environmental epigenetics. Heredity 105 (1), 105–112.
Caraci, F., Calabrese, F., Molteni, R., Bartova, L., Dold, M., Leggio, G.M., Fabbri, C., Mendlewicz, J., Racagni, G., Kasper, S., Riva, M.A., Drago, F., Ohlstein, E.H., 2018. International union of basic and clinical pharmacology CIV: the neurobiology of treatment-resistant depression: from antidepressant classifications to novel pharmacological targets. Pharmacol. Rev. 70 (3), 475–504.
Chang, M., He, L., Cai, L., 2018. An overview of genome-wide association studies. In: Computational Systems Biology. Humana Press, New York, NY, pp. 97–108.
Chen, D., Meng, L., Pei, F., Zheng, Y., Leng, J., 2017. A review of DNA methylation in depression. J. Clin. Neurosci. 43, 39–46.
Cui, R., 2015. Editorial: A systematic review of depression. Curr. Neuropharmacol. 13 (4), 480.
Dalton, V.S., Kolshus, E., McLoughlin, D.M., 2014. Epigenetics and depression: return of the repressed. J. Affect. Disord. 155, 1–12.
Edvardsen, J., Torgersen, S., Røysamb, E., Lygren, S., Skre, I., Onstad, S., Øien, P.A., 2009. Unipolar depressive disorders have a common genotype. J. Affect. Disord. 117 (1–2), 30–41.
El-Saadony, M.T., Abd El-Hack, M.E., Swelum, A.A., Al-Sultan, S.I., El-Ghareeb, W.R., Hussein, E.O.S., Ba-Awadh, H.A., Akl, B.A., Nader, M.M., 2021c. Enhancing quality and safety of raw buffalo meat using the bioactive peptides of pea and red kidney bean under refrigeration conditions. Ital. J. Anim. Sci. 20 (1), 762–776.
El-Saadony, M.T., Elsadek, M.F., Mohamed, A.S., Taha, A.E., Ahmed, B.M., Saad, A.M., 2020. Effects of chemical and natural additives on cucumber juice's quality, shelf life, and safety. Foods 9 (5), 639.
El-Saadony, M.T., Khalil, O.S., Osman, A., Alshilawi, M.S., Taha, A.E., Aboelenin, S.M., Shukry, M., Saad, A.M., 2021b. Bioactive peptides supplemented raw buffalo milk: biological activity, shelf life and quality properties during cold preservation. Saudi J. Biol. Sci. 28 (8), 4581–4591.
El-Saadony, M.T., Saad, A.M., Elakkad, H.A., El-Tahan, A.M., Alshahrani, O.A., Alshilawi, M.S., Ahmed, A.I., 2022. Flavoring and extending the shelf life of cucumber juice with aroma compounds-rich herbal extracts at 4°C through controlling chemical and microbial fluctuations. Saudi J. Biol. Sci. 29 (1), 346–354.
El-Saadony, M.T., Saad, A.M., Taha, T.F., Najjar, A.A., Zabermawi, N.M., Nader, M.M., AbuQamar, S.F., El-Tarabily, K.A., Salama, A., 2021d. Selenium nanoparticles from *Lactobacillus paracasei* HM1 capable of antagonizing animal pathogenic fungi as a new source from human breast milk. Saudi J. Biol. Sci. 28 (12), 6782–6794.
El-Saadony, M.T., Zabermawi, N.M., Zabermawi, N.M., Burollus, M.A., Shafi, M.E., Alagawany, M., Abd El-Hack, M.E., 2021a. Nutritional aspects and health benefits of bioactive plant compounds against infectious diseases: a review. Food Rev. Int., 1–23 https://doi.org/10.1080/87559129.2021.1944183.
Ettman, C.K., Abdalla, S.M., Cohen, G.H., Sampson, L., Vivier, P.M., Galea, S., 2020. Prevalence of depression symptoms in US adults before and during the COVID-19 pandemic. JAMA Network Open 3 (9), e2019686.
Franić, S., Middeldorp, C.M., Dolan, C.V., Ligthart, L., Boomsma, D.I., 2010. Childhood and adolescent anxiety and depression: beyond heritability. J. Am. Acad. Child Adolesc. Psychiatry 49 (8), 820–829.
Gałecki, P., Samochowiec, J., Mikułowska, M., Szulc, A., 2022. Treatment-Resistant Depression in Poland—Epidemiology and Treatment. J. Clin. Med. 11, 480. https://doi.org/10.3390/jcm11030480.
Gibney, E.R., Nolan, C.M., 2010. Epigenetics and gene expression. Heredity 105 (1), 4–13.
Gold, P.W., Machado-Vieira, R., Pavlatou, M.G., 2015. Clinical and biochemical manifestations of depression: relation to the neurobiology of stress. Neural Plast. 2015. https://doi.org/10.1155/2015/581976.
Guo, J.U., Su, Y., Shin, J.H., Shin, J., Li, H., Xie, B., Zhong, C., Hu, S., Le, T., Fan, G., Zhu, H., Chang, Q., Gao, Y., Ming, G.-l., Song, H., 2014. Distribution, recognition and regulation of non-CpG methylation in the adult mammalian brain. Nat. Neurosci. 17 (2), 215–222.
Horowitz, M.A., Taylor, D., 2019. Tapering of SSRI treatment to mitigate withdrawal symptoms. Lancet Psychiatry 6 (6), 538–546.
Isles, A.R., 2018. Epigenetics, chromatin and brain development and function. Brain Neurosci. Adv. 2 (5984). 239821281881201.
Isles, A.R., 2015. Neural and behavioral epigenetics; what it is, and what is hype. Genes Brain Behav. 14 (1), 64–72.
Kuehner, J.N., Bruggeman, E.C., Wen, Z., Yao, B., 2019. Epigenetic regulations in neuropsychiatric disorders. Front. Genet. 10. https://doi.org/10.3389/fgene.2019.00268.
Kupfer, D.J., Frank, E., Phillips, M.L., 2012. Major depressive disorder: new clinical, neurobiological, and treatment perspectives. Lancet (London, England) 379 (9820), 1045–1055.
Mann, J.J., Currier, D., 2006. Effects of genes and stress on the neurobiology of depression. International review of neurobiology 73, 153–189.
Mill, J., Petronis, A., 2007. Molecular studies of major depressive disorder: the epigenetic perspective. Mol. Psychiatry 12 (9), 799–814.
Moore, D.S., 2015. The Developing Genome: An Introduction to Behavioral Epigenetics. Oxford University Press.
Moosavi, A., Ardekani, A.M., 2016. Role of Epigenetics in biology and human diseases. Iran. Biomed. J. 20 (5), 246–258.
Naismith, S.L., Norrie, L.M., Mowszowski, L., Hickie, I.B., 2012. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Progress in neurobiology 98 (1), 99–143.
Natale, A., Mineo, L., Fusar-Poli, L., Aguglia, A., Rodolico, A., Tusconi, M., Amerio, A., Serafini, G., Amore, M., Aguglia, E., 2022. Mixed depression: A mini-review to guide clinical practice and future research developments. Brain Sci. 12, 92. https://doi.org/10.3390/brainsci12010092.
National Collaborating Centre for Mental Health (UK), 2010. The management of subthreshold depressive symptoms. In Depression: The Treatment and Management of Depression in Adults (Updated Edition). British Psychological Society.
Nestler, E.J., 2014. Epigenetic mechanisms of depression. JAMA Psychiatry 71 (4), 454.
Nestler, E.J., Barrot, M., DiLeone, R.J., Eisch, A.J., Gold, S.J., Monteggia, L.M., 2002. *Neurobiology of depression*. Neuron 34 (1), 13–25.
Palazidou, E., 2012. The neurobiology of depression. ritish medical bulletin 101 (1), 127–145.
Phillips, C., 2017. Physical activity modulates common neuroplasticity substrates in major depressive and bipolar disorder. Neural Plasticity 71 (4), 454–456. https://doi.org/10.1001/jamapsychiatry.2013.4291.
Reda, F.M., El-Saadony, M.T., El-Rayes, T.K., Attia, A.I., El-Sayed, S.A., Ahmed, S.Y., Alagawany, M., 2021b. Use of biological nano zinc as a feed additive in quail nutrition: biosynthesis, antimicrobial activity and its effect on growth, feed utilisation, blood metabolites and intestinal microbiota. Italian Journal of Animal Science 20 (1), 324–335.
Reda, F.M., El-Saadony, M.T., El-Rayes, T.K., Farahat, M., Attia, G., Alagawany, M., 2021a. Dietary effect of licorice (*Glycyrrhiza glabra*) on quail performance, carcass, blood metabolites and intestinal microbiota. Poultry Science 100 (8), 101266.
Saad, A.M., Elmassry, R.A., Wahdan, K.M., Ramadan, F.M., 2015. Chickpea (*Cicer arietinum*) steep liquor as a leavening agent: effect on dough rheology and sensory properties of bread. Acta Periodica Technol. 46, 91–102.
Saad, A.M., El-Saadony, M.T., Mohamed, A.S., Ahmed, A.I., Sitohy, M.Z., 2021a. Impact of cucumber pomace fortification on the nutritional, sensorial and technological quality of soft wheat flour-based noodles. Int. J. Food Sci. Technol. 56, 3255–3268. https://doi.org/10.1111/ijfs.14970.
Saad, A.M., Sitohy, M.Z., Ahmed, A.I., Rabie, N.A., Amin, S.A., Aboelenin, S.M., Soliman, M.M., El-Saadony, M.T., 2021b. Biochemical and functional characterization of kidney bean protein alcalase-hydrolysates and their preservative action on stored chicken meat. Molecules 26 (15), 4690.
Saavedra, K., Molina-Márquez, A.M., Saavedra, N., Zambrano, T., Salazar, L.A., 2016. Epigenetic modifications of major depressive disorder. Int. J. Mol. Sci. 17 (8), 1279.
Salik, I., Marwaha, R., 2021. Stat Pearls [Internet]. Stat Pearls Publishing; Treasure Island (FL): Sep 21, 2021. Electroconvulsive Therapy.
Shadrina, M., Bondarenko, E.A., Slominsky, P.A., 2018. Genetics Factors in major depression disease. Front. Psychiatry 9, 334. https://doi.org/10.3389/fpsyt.2018.00334.
Shadrina,, M., Bondarenko, E.A., Slominsky, P. A., 2018. Genetics factors in major depression disease. Frontiers in psychiatry 9, 334.
Soga, T., Teo, C.H., Parhar, I., 2021. Genetic and epigenetic consequence of early-life social stress on depression: Role of serotonin-associated genes. Front. Genet. 1757. https://doi.org/10.3389/fgene.2020.601868.
Uchida, S., Yamagata, H., Seki, T., Watanabe, Y., 2018. Epigenetic mechanisms of major depression: targeting neuronal plasticity. Psychiatry Clin. Neurosci. 72 (4), 212–227.
Vialou, V., Feng, J., Robison, A.J., Nestler, E.J., 2013. Epigenetic mechanisms of depression and antidepressant action. Annu. Rev. Pharmacol. Toxicol. 53 (1), 59–87.
Yaqoob, M.U., El-Hack, M.E.A., Hassan, F., El-Saadony, M.T., Khafaga, A.F., Batiha, G. E., Yehia, N., Elnesr, S.S., Alagawany, M., El-Tarabily, K.A., Wang, M., 2021. The potential mechanistic insights and future implications for the effect of prebiotics on poultry performance, gut microbiome, and intestinal morphology. Poult. Sci. 100 (7), 101143.
Zahavi, A.Y., Sabbagh, M.A., Washburn, D., Mazurka, R., Bagby, R.M., Strauss, J., Kennedy, J.L., Ravindran, A., Harkness, K.L., Sgambato-Faure, V., 2016. Serotonin and dopamine gene variation and theory of mind decoding accuracy in major depression: A preliminary investigation. PloS One 11 (3), e0150872.
Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., Sheehan, J.J., 2021. The prevalence and national burden of treatment-resistant depression and major depressive disorder in the United States. J. Clin. Psychiatry 82 (2), 29169.