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*REVIEW*

# Resilience by design: How nature, nurture, environment, and microbiome mitigate stress and allostatic load

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## Abstract

Resilience to psychological stress is defined as adaption to challenging life experiences and not the absence of adverse life events. Determinants of resilience include personality traits, genetic/epigenetic modifications of genes involved in the stress response, cognitive and behavioral flexibility, secure attachment with a caregiver, social and community support systems, nutrition and exercise, and alignment of circadian rhythm to the natural light/dark cycle. Therefore, resilience is a dynamic and flexible process that continually evolves by the intersection of different domains in human's life; biological, social, and psychological. The objective of this minireview is to summarize the existing knowledge about the multitude factors and molecular alterations that result from resilience to stress response. Given the multiple contributing factors in building resilience, we set out a goal to identify which factors were most supportive of a causal role by the current literature. We focused on resilience-related molecular alterations resulting from mind-body homeostasis in connection with psychosocial and environmental factors. We conclude that there is no one causal factor that differentiates a resilient person from a vulnerable one. Instead, building resilience requires an intricate network of positive experiences and a healthy lifestyle that contribute to a balanced mind-body connection. Therefore, a holistic approach must be adopted in future research on stress response to address the multiple elements that promote resilience and prevent illnesses and psychopathology related to stress allostatic load.

**Key Words:** Resilience; Stress; Allostatic load; Epigenetics; Circadian rhythm; Attachment; Oxytocin; Diet; Microbiome; Exercise

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**Core Tip:** There are multiple reviews in the literature that address different factors contributing to resilience, an adaptation to stress. To our knowledge, none of these reviews takes into consideration the complexity of the system that leads to allostasis or allostatic load, an indicator of physiologic "wear and tear" resulting from repeated exposure to stress and inability to cope. The purpose of this review is to shed light on the complexity of the system and discuss the molecular mechanisms that may contribute to resilience. Lastly, we conclude by emphasizing the need for a comprehensive approach to reduce stress allostatic load.

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## INTRODUCTION

According to the American Psychological Association (APA), "resilience is the process and outcome of successfully adapting to difficult or challenging life experiences, especially through mental, emotional, and behavioral flexibility and adjustment to external and internal demands". Adaptation to adversities depends on several factors: Individual's engagement and view of the world, the availability of social and communal resources, and the use of specific coping strategies (APA, 2022, https://www.apa.org/topics/resilience). It is worth noting that resilience and coping are inter-related but have different constructs with respect to their impact on behavioral changes[1]. While coping manages stressful events by using cognitive and behavioral strategies[2], resilience refers to the adaptive capacity to recover from traumatic or stressful situations[3].

Research in humans over the last two decades has demonstrated that resilience and use of adaptive coping skills in the face of adversity in both children and adults are the main factors that protect from developing mental and physical illnesses. While personal characteristics such as personality traits of persistence and determination, and cognitive flexibility are key elements, perceived parental care, adolescent peer relationships, adult romantic relationships, community support systems, dietary lifestyle, exercise, and circadian rhythm are all implicated in building resilience[4-11]. Resilience is an active adaptive process that helps mitigate negative social, psychological, and biological consequences of extreme stress[12]. The adaptive behavioral manifestations of resilient people are described as enhanced internal locus of control, self-efficacy, happiness, life satisfaction, the ability to derive a sense of life meaning, ability to foster social and communal interactions, and problem-solving skills[13,14].

Fostering resilience early in life may be an effective preventative measure prior to the development of trauma[15]. It is estimated that 60% of men and 50% of women would experience at least one potentially traumatic event in their lifetime, however only 8% of women and 4% in men develop post-traumatic stress disorder (PTSD) (National Center of PTSD, 2022, https://www.ptsd.va.gov/). The development of resilience is an ongoing dynamic process throughout the lifespan in both children and adults, even in those who have suffered from adverse early life experiences, to successfully adapt to or overcome traumatic stress-related illnesses[16,17]. Indeed, resilience can aid in developing positive changes in the aftermath of traumatic events, such as gaining the capacity to relate to others, personal strength, spirituality, and life appreciation[18]. Resilience is implicated in changes in brain regions involved with the social networks that promote empathy, social connectedness, and modulation of central responses to stress[19].

The objective of this review is to summarize the existing knowledge about the multitude factors and molecular alterations that result from resilience to stress response. Our aim is to create awareness for future research studies on allostatic load and stress response about the intricate network contributing to resilience. The methodology we used is Literature Review performed through PubMed, PsycINFO and Scopus databases for peer-reviewed English-language articles published prior to December 2022 using the following keywords: Chronic stress, allostatic load, trauma, biomarkers, circadian rhythm, resilience, neurobiology, genetic, epigenetic, attachment, oxytocin, gut microbiome, diet, mindfulness, exercise, and psychotherapy. We will first describe the existing knowledge about the biologic aspects of the stress response and implications of chronic stress. Then we will present the different factors that contribute to resilience and associated molecular changes.

## STRESS RESPONSE AND HYPOTHALAMIC-PITUITARY-ADRENAL ACTIVATION

### *The neurohormonal mechanism of stress response*

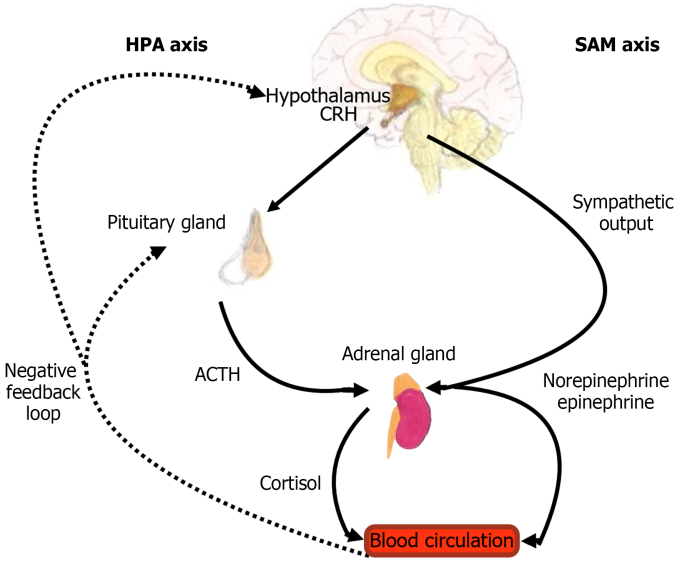
The stress response involves a neurohormonal mechanism activated by the cross talk of the hypothalamic-pituitary-adrenal (HPA)-axis and the sympathetic-adrenal-medullary (SAM)-axis that results in widespread hormonal, neurochemical, and physiological alterations. The SAM axis activates the peripheral sympathetic nervous system to release epinephrine and norepinephrine[20,21]. HPA axis activation leads to a cascade of events whereby corticotropin releasing hormone released from the hypothalamus stimulates the release of adrenocorticotropic (ACTH) from the pituitary gland, which in turn results in production of glucocorticoids (GCs) from the adrenal cortex. GCs, also known as cortisol in mammals and corticosterone in rodents, regulate cellular function by interacting with steroid receptors that modulate the neural circuitry and neuroendocrine systems involved in behavioral responses to stress[21]. These receptors, glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), are expressed throughout the brain, mostly in the prefrontal cortex (PFC), hippocampus, amygdala, and other limbic and midbrain structures[17,22]. Under conditions of threat, HPA activation leads to increased release of GCs to promote acute survival by mobilizing stored energy, hence contributing to a state of increased arousal and vigilance. The stress response is then terminated by a negative feedback loop that attenuates the HPA-axis at the level of GR, causing GCs levels to return to normal (Figure 1)[23]. In contrast to GR, MR modulates basal and stress-induced HPA-axis activity to appraise stress and fear-related memories. Enhanced expression and function of MR may improve resilience to traumatic stress and reduces the risk for psychiatric disorders[21]. Studies have shown that MR dampen glucocorticoid receptor sensitivity to stress *via* regulation of FK506-binding protein 5 (FKBP5), a potent negative regulator of glucocorticoid signaling that plays an important role in fine-tuning the MR:GR balance in the hippocampus[24].

When the HPA axis is activated, dehydroepiandrosterone (DHEA) is also released by the adrenal glands along with GCs. DHEA is an important mediator of the HPA axis since it facilitates the N-methyl-D-aspartate receptor function, antagonizes g-Aminobutyric Acid A receptors, and facilitates metabolism of cortisol to the inactive metabolite cortisone. DHEA-Sulfate (DHEA-S), a more potent form than DHEA, plays a neuroprotective role by inhibiting GC effects at the level of the GR as well as supporting neurogenesis[25-28]. Cortisol/DHEA-S ratio represents a balance between the catabolic effects of cortisol and the anabolic, regenerative function of DHEA-S[27,29]. In fact, a higher DHEA-S to cortisol ratio predicted stress resilience in male military personnel, lowering symptoms of PTSD and showing greater improvement over time[30]. On the other hand, a lower resting DHEA/cortisol ratio has been associated with childhood trauma[26].

### *Circadian control of the HPA axis*

Multiple studies have demonstrated the close connection between the circadian rhythm and stress systems to maintain allostasis. The homeostasis of the HPA axis, which produces the primary mediators in adaptation to stress, is closely regulated by the circadian rhythm output[31]. The nearly 24-h periodic peripheral rhythms are controlled by the master circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN). The SCN generates a daily rhythm of transcription and translation feedback loop that align with the 24-h external light-dark environment[32]. The central clock in the SCN orchestrates peripheral clocks at the cellular level to synchronize physiological and behavioral rhythms and regulates the activity of various humoral and neuronal allostatic mediators, among which GCs that show a robust time-of-day dependence[33-35]. These robust circadian dynamics of the allostatic mediators enable the host to flexibly respond and adapt to various physiological stressors[36,37]. In this current modern society and lifestyle that humans live in, where light at night is widespread due to adoption of electrical light, we developed a deranged temporal adaptation that our physiological systems have not evolved to cope with. The chronic disruption of circadian rhythms predisposes to physiologic and behavioral changes that can lead to maladaptive allostatic mechanisms and compromising resilience[32,36].

Animal studies have shown that disruption of the circadian rhythm by misalignment to the natural light/dark cycle in mice results in neurobehavioral changes resulting in decreased complexity of neurons in the prefrontal cortex, the brain center involved in executive and emotional control, and reduction in cognitive flexibility[38]. Even short-term circadian misalignment has been shown to disrupt memory consolidation in response to fear-conditioning that could compromise resilience[39]. The bidirectional communication between the central clock and HPA axis is also evident by circadian disruption in response to early life stress that contributes to metabolic derangement occurring later in life[40]. Hence, re-alignment of circadian rhythms by following the natural light/dark cycle can enhance allostatic adaptive resilience and can be especially beneficial for individuals with psychiatric disorders who struggle with sleep disturbances[41-43]. Interestingly, timing of Trauma Exposure therapy to specific trauma-associated cues can have a different outcome in the process of healing. One study found that exposure to trauma cues is more efficacious when administered during the morning time compared to the evening[44,45].




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**Figure 1 Hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes, neurohormonal output, and feedback loop.** CRH: Corticotropin releasing hormone; HPA: Hypothalamic-pituitary-adrenal; SAM: Sympathetic-adrenal-medullary; ACTH: Adrenocorticotropic; ACTH: Adrenocorticotropic hormone.

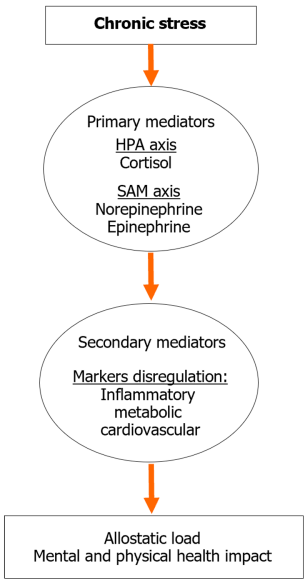
### *Chronic stress and allostatic load*

As presented above, exposure to stress triggers several biological mechanisms in the body that release stress hormones as primary mediators in order to adapt to short term or acute stress. Maintaining stability through change is a phenomenon known as allostasis[46,47]. Allostasis is considered a beneficial adaptive mechanism that promotes host survival through the appropriate activation of energetic resources[48]. However, repeated exposure to stress, also known as chronic stress, can result in prolonged activation of the HPA and SAM axes, which may lead to activation of secondary inflammatory and metabolic mediators, and ultimately lead to deleterious effect on metabolic, immune, and cardiovascular functions as well as brain and behavior (Figure 2)[49-52]. The cumulative effects of chronic stress reduce the ability of the host to flexibly cope with subsequent stressful situations, which lead the system to shift from allostasis to allostatic load or physiological "wear and tear"[53-56].

### *Impact of chronic stress on brain and gene expression*

While it is beyond the scope of this minireview to discuss all the structural, biological and genetic modifications in response to chronic or developmental stress, we will briefly discuss few structural changes and gene variants involved in the stress response, which may result in either negative or positive associations to resilience. Animal studies have shown structural changes in different brain regions whereby chronic stress increases dendritic spine number or branching in the amygdala and nucleus accumbens, reduces dendritic arborization and glutamatergic dendritic spine density of pyramidal neurons in PFC and hippocampus, and decreases hippocampus neurogenesis[57].

The impact of the environment and specifically early life stress profoundly alters key genes involved in stress response *via* epigenetic modification. Many of these genes can be modified through epigenetic alterations and variation in microRNAs (miRNA), short non-coding RNAs detected in body fluids, in response to environmental influences[58,59]. Little is known about the role of miRNA in psychiatric disorders and resilience. One animal study showed that the systemic knockdown of miRNA-144-3p reduced the depression-like phenotype in stress-susceptible mice[60]. Another study demonstrated that knockdown of miRNA-144 and miRNA-33 in the hippocampus increased the proportion of resilient female animals[61]. Studies also showed that low maternal care is associated with epigenetic modification by increased methylation of the gene encoding GR (*NR3C1*), leading to decreased GR expression in the hippocampus[62,63]. Another important player in regulating the stress response is the *FKBP5* gene. This gene modulates intracellular glucocorticoid signaling and homeostatic regulation of the stress response[64]. Studies have shown that epigenetic modifications induced by early life stress or single nucleotide polymorphisms (SNPs) in human *FKBP5* gene result in differential induction of the FKBP5 protein upon glucocorticoid stimulation, thereby adding to the variability of stress perception and response, and increasing the risk of developing stress-related psychiatric disorders[65,66].




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**Figure 2 Impact of chronic stress on allostatic load mediated by primary and secondary biomarkers.** HPA: Hypothalamic-pituitary-adrenal; SAM: Sympathetic-adrenal-medullary.

## FACTORS CONTRIBUTING TO BUILDING RESILIENCE

### *Role of psychosocial interventions: Brain and epigenetic alterations*

While early-life stress can induce permanent changes in behavioral and physiological responses to stress through epigenetic modification, DNA methylation is potentially reversible through intervention. Using blood samples from human, methylation levels of specific regions within *FKBP5* and brain derived neurotrophic factor (*BDNF*) were changed in response to psychotherapy and were associated with recovery and improvement[67,68]. For example, Exposure-based Cognitive Behavioral Therapy results in a decrease in *FKBP5* methylation and leads to a positive treatment response[69]. Furthermore, maternal stroking and tactile stimulation can normalize DNA methylation in the leukocytes of infants who had been exposed to high levels of pre- and postnatal maternal depression[70]. Mindfulness practice is well known to improve cognitive and social functioning, and reduce symptoms of depression and anxiety[71,72]. The mechanisms whereby mindfulness regulates the stress response is through activation of brain regions involved in interoception, self-awareness, emotion regulation, and threat detection[73-75]. Mindfulness practice has been shown to alter different immune and endocrine pathways, as well as epigenetic methylation of the *FKBP5* gene in adults with PTSD[76-78].

These findings are in line with animal studies demonstrating that intervention by enrichment can reverse the epigenetic, plasticity, and behavioral deficits in rats exposed to early life stress[79]. Indeed, our group has recently published a new treatment approach, Cue Centered Therapy (CCT) for complex developmental trauma in children and adolescents. CCT emphasizes resiliency and positive adaptation factors by using the life timeline as a core component for both positive and negative events in youth's life. CCT has shown effectiveness in improving functioning and reducing child and parent post-traumatic stress. Treatment outcome research of CCT have demonstrated PTSD symptom improvement as measured by cortical activation patterns using functional near-infrared spectroscopy, a non-invasive neuroimaging technique[80,81].

### *Role of oxytocin and attachment*

Another important molecular determinant of resilience is oxytocin (OXT), which is closely tied to attachment. Humans are considered social mammals that develop various forms of social attachments and bonds from infancy throughout life[82,83]. The influence of secure attachment to a caregiver modulates physiology and behavior and is essential for a healthy psychological development and well-being. Attachment is a psychological/behavioral construct for infant's self-regulation that is promoted and facilitated by caregiver's ongoing emotional availability. Infants internalize their interactions with their caregiver and build internal working models that represent their attachment figures in relation to themselves[82]. Attachment styles during early life predict moderate stability of attachment over the years but can be susceptible to change by significant relationship experiences[84]. The different attachment styles are believed to have a profound shaping of an individual's emotional and psychosocial functioning as well as resilience or predisposition to psychopathology[85-87].

It is established that sudden separation of children from their parents, interpreted as abandonment, threatens the attachment bond and results in profound sense of shame and complex emotions especially in the absence of adequate support[88,89]. In addition to the impact of separation on secure attachment, transgenerational maternal experiences with unresolved attachment to their own caregivers can influence the quality of bonding of those mothers to their children. Children of mothers who exhibit higher distress and disruptive behavior exhibited a significantly higher cortisol compared to ones with no disruptive behavior[90]. These differences in cortisol levels and behavior may be related to gene polymorphism of the OXT and OXT receptor (OXT-R) in children from mothers with negative maternal experiences. These genes moderate the stress response of children, and polymorphisms can be associated with the disorganized behavior independent of maternal experiences[91].

The OXT system activated through social interaction is thought to have an important implication in building resilience by playing an important role in the regulation of affective and social behaviors as well as modulating stress response[92-94]. OXT is a neuropeptide produced by hypothalamic paraventricular, supraoptic, and accessory nuclei, and is released to the posterior pituitary gland and ultimately to the peripheral blood circulation[95,96]. In addition to OXT's role in parturition and lactation[97], the neuropeptide plays a key role in promotion of postnatal sensitive maternal caregiving to optimize infant's social and emotional development[98-100]. Higher levels of OXT have been linked with increased attention to social cues[101] while lower levels have been seen in maltreated children [102]. A positive association between OXT level and interpersonal bonding and affiliation, as well as stress modulation in interpersonal situations is well established. In animal models, OXT facilitates mating-induced pair bonds *via* mesolimbic dopamine system, however, variation in striatal OXT-R density predicts resilience and susceptibility to neonatal social neglect[103,104]. Growing evidence from animal and human studies showed that OXT signaling early in life by parental nurturing can buffer against physical and emotional stressors and help establish the neural networks needed during adult life to form social bonds[105-110].

Maternal care during early life, which overlaps with behaviors involving OXT in mother and infant through embedded hidden regulators, maintains the stress hyporesponsive period and direct HPA maturation during heightened plasticity[62]. It has been established that early life stress in human and non-human primates is associated with changes in cerebrospinal fluid OXT level and social behavior, as well as the ability of parental presence to attenuate stress response to a novel environment[111-113]. Animal studies have shown that OXT controls the secretion of ACTH under stress condition and enhance the long-term HPA axis response to stress in adult rats, which may act as a feedback regulator to enhance recovery from stress-related symptoms[114-116].

OXT seems to play an important role in fear modulation where it strengthens fear memory to predictable or cued fear while attenuating fear memory to unpredictable, diffuse threats (contextual fear and non-cued fear)[117-122]. Thus, OXT fosters adaptive defensive behaviors and accurate fear discrimination of relevant and imminent threats, yet reducing sustained fear responses to distant threats[123]. Animal studies have shown that administration of OXT by intracerebroventricular injection or intranasally facilitated cued fear extinction and reduced chronic stress-induced deficits in fear extinction in male rats, respectively. In contrast, administration of OXT-R antagonist impaired fear extinction in male rats[124,125]. These studies emphasized the role of OXT in reducing sustained fear responses and anxiety-like behaviors while strengthening fear responses to relevant and predictable threats. Nuclei of the central amygdala are the main output that connect to the brainstem to eventually mediate the fear response, including freezing behavior. OXT-R transmission in the amygdala switches from passive freezing to active escape behaviors in confrontation with an imminent, but escapable threat[126-128]. OXT also mediates affiliate and prosocial behaviors. OXT-R signaling facilitates social transmission of fear between familiar conspecifics, which might serve as warning system of impeding threat[129,130].

SNPs of the OXT-R gene, rs53576, has been shown to be associated with individual differences in social and emotional abilities, predisposition to psychopathology, and environmental adversity in the prediction of anxiety and depression[131-138]. Human brain-imaging studies in repeated childhood trauma and emotional neglect have demonstrated structural and functional variations in the amygdala, hypothalamus and cingulate gyrus in response to OXT-R gene polymorphism leading to variations in social and behavioral outcomes[139]. Furthermore, epigenetic alterations to specific OXT-R gene polymorphisms can attenuate resting parasympathetic tone and increasing central amygdala grey volume, thereby altering traumatic stress reactivity[140].

### *Role of diet, gut microbiome, and exercise*

There is an extensive connection between the mind and body in which the wellbeing of one influences the other. A major element of this mind-body connection is the brain-gut axis. Indeed, there is an association between early life adversities and changes in the brain-gut axis that may occur *via* pathways related to glutamatergic excitotoxicity and oxidative stress, predisposing to negative mood and stress [141].

**Maternal diet and resilience:** The quality of dietary interventions during a critical period of neural development predicts the function of the brain-gut axis and plays a key role in building resilience to stress. Earlier studies showed that maternal nutrition during pregnancy plays a fundamental role in

intrauterine developmental programming and predicts child's resilience to stress and vulnerability to psychiatric disorders, such as anxiety and depression. Maternal malnutrition during fetal development has a detrimental long-term impact on the physical, cognitive, and emotional development[142,143]. A deficit in maternal dietary protein during pregnancy alters the brain neurochemistry and behavior by reducing 5-hydroxytryptamine 1A receptor and the responsiveness to stress during adult life[144]. It has been shown that branched-chain amino acids such as leucine, isoleucine or valine are essential nutrients that promote resilience *via* activation of hippocampal BDNF signaling[145]. An unbalanced diet during pregnancy is linked to heightened HPA axis responses to stress and higher cortisol levels as well as epigenetic changes in genes controlling glucocorticoid action in adult offspring[146-148].

**Microbiome and gut-brain axis:** The gut microbiota plays a major role in shaping how the body responds to stress. Animal studies have shown that Germ-free mice with absent microbiota have significant variations in their stress response caused by abnormal development of the HPA axis that was reversed by inoculation of Bifidobacteria infantis[149]. Exposure to early life adversity is correlated with changes in microbial diversity of the gut where taxonomic abundances predicted PFC activity[150].

The microbiome-derived short-chain fatty acids (SCFA) are the most studied metabolites because they ameliorate the gut-brain axis and stress-induced cortisol release in humans and rodents[151]. The composition of diet is essential because it can impact gut-brain pathways involved in stress response. A healthy diet rich in fibers, phytochemicals, or live bacteria can increase microbial diversity and enhances production of SCFA and other bioactive compounds[152,153]. Western diet, lacking in dietary fibers, is associated with suboptimal gut microbiota composition and a low-grade systemic inflammation that can predispose to mental illness, gastrointestinal and metabolic disorders, and obesity[154,155]. In addition to diet, exercise has been shown to increase SCFA availability, thereby influencing microbiome composition[156]. Gut microbes also play a major role in synthesizing key neuroactive molecules such as serotonin, gamma-aminobutyric acid, and catecholamines like norepinephrine and dopamine. For example, *Lactobacillus* can stimulate the conversion of dietary tryptophan into 5-hydroxytryptamine by enterochromaffin cells, which then interacts with the autonomic nervous system and conveys the signal to other brain structures, such as the hypothalamus, nucleus accumbens, and ventral tegmental area [157-159].

Microbiome-targeted therapies known as "psychobiotics" that include administration of live organisms, fecal microbial transplants, and dietary interventions to reshape the microbiome composition and function have beneficial effects on brain and behavior[152,160,161]. Administration of the probiotic organisms *Bifidobacterium* and *Lactobacillus* is known to confer resilience in social defeat model and has been tested in clinical depression[161,162]. Additionally, probiotics supplementation results in higher DHEA-to-corticosterone fecal metabolite ratios and reduces microglia immunoreactivity in the basolateral amygdala in rodent models, thereby mitigating the pervasive effects of early life stress on anxiety and depressive behavior as well as HPA axis activity[163].

Modulating the microbiota–gut–brain-axis through diet is also a promising approach to prevent and treat mental health disorders. Consumption of a Mediterranean diet resulted in a significant improvement in depressive symptoms after 12 weeks of dietary intervention compared to control group among patients with major depressive disorder[164,165]. Studies have also shown that adherence to Mediterranean diet, consumption of fruits and vegetable-based dietary pattern and dietary polyphenols were positively associated with psychological resilience[166]. Polyphenols are stress-modifying phytochemicals composed of hydroxylated phenyl moieties and are abundant in fruits, vegetables, tea, caffeine, curcumin, herbs, citrus peel, and grape seeds. They have anti-inflammatory actions, which may be involved in fighting psychosocial stress. Therefore, polyphenols are considered adaptogens (stress response modifiers that have beneficial effects to protect from chronic diseases) because of their ability to adapt to and survive external stressors[167-171]. Polyphenols are also considered 'prebiotics' because of their ability to enhance the growth of specific beneficial bacteria that produce bioactive phenolic acids, which promotes cognitive resilience to depression and anxiety[172-175].

**Exercise and resilience:** Exercise is well known for its benefit in enhancing resilience and longevity. Physical activity through exercise activates endocrine, paracrine, and autocrine pathways through the release of exerkines (signaling particles that have a potential role in improving health in response to exercise), cytokines, nucleic acids, lipids, and metabolites from multiple organs[176]. Exercise is well known to improve brain function, most notably the effect on learning and memory. Indeed, aerobic exercise increases hippocampal volume and improves memory, increases plasma levels of BDNF, and delays the onset of neuro-degenerative conditions in older adults human studies[177-179]. These findings are in line with animal studies on rodents where chronic exercise resulted in upregulation of BDNF in the hippocampus, leading to hippocampal neurogenesis, neural plasticity, and improved cognition and mood[180]. A possible mechanism of the upregulation of BDNF in hippocampus is through the release of irisin from myokines, which plays an important role in hippocampal neurogenesis, increased neurotrophin levels, and enhanced mood and cognition[181]. Another benefit of exercise is the release of adiponectin from adipocyte that seems to have neuroprotective effects by crossing the blood–brain barrier and resulting in increased neurogenesis and reduced depression-like behaviors[182]. Kynurenic acid, another molecule of interest produced in muscles in response to chronic

aerobic exercise, has been shown to protect the brain from stress-induced depression[183]. Vigorous exercise is also associated with lower emotional distress, depression, and anxiety[184,185].

Studies have linked the adaptative changes in opioid systems to regular exercise, which reduces noradrenergic-induced stress responses. Regular exercise activates the endogenous opioid in the peripheral and central nervous system and is implicated in mood improvement[186,187]. The stress-reducing effect of exercise in response to both physical and psychological challenge is reversed by administration of naloxone, an opioid antagonist[188,189].

## DISCUSSION

We have addressed in this minireview the biological basis of resilience as an outcome of structural and molecular alterations resulting from various determinants. Understanding the molecular aspect of resilience can provide insight for therapeutic discoveries and interventions to promote resilience in face of adverse life events. Here we showed that building resilience requires an intricate network of positive experiences and healthy lifestyle that contribute to a balanced mind-body connection (Figure 3). Indeed, positive childhood experiences such as interpersonal social and emotional support can mitigate the impact of adverse childhood experiences, thereby reducing the risk for adult onset depression and poor mental health[190].

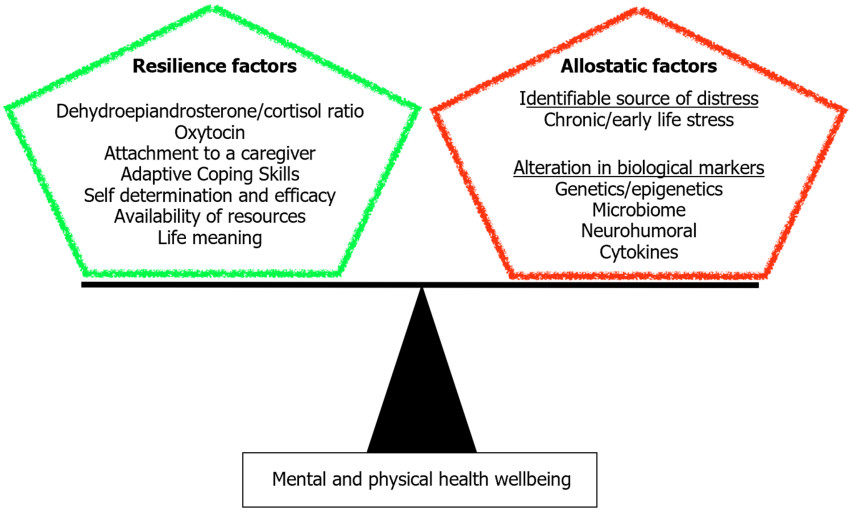
Clinical and preclinical investigations showed that resilience is implicated in molecular alterations and changes in brain regions involved with the social networks that promote empathy, social connectedness, and modulation of central responses to stress. DNA methylation in response to early life stress is potentially reversible through intervention. Resilience promoted by psychotherapy and mindfulness practices reverses the epigenetic modification of *FKBP5* and *BDNF* genes caused by stress response and alters cortical activation to improve PTSD symptoms[76-78,80,81]. Investigations also showed that DHEA-S, OXT and enhanced expression of MR can be used as important predictors of resilience[21,24,30]. OXT, a neuropeptide tied to attachment, plays a key role in promotion of postnatal sensitive maternal caregiving to optimize infant's social and emotional development and establish the neural networks needed during adult life to form social bonds[105-110]. OXT is also a feedback regulator of the HPA axis that enhance recovery from stress-related symptoms[114].

Recent studies also showed the association between early life adversities and circadian rhythm disruption as well as changes in brain-gut axis that may occur *via* pathways related to glutamatergic excitotoxicity and oxidative stress, predisposing to metabolic derangement, negative mood and stress [37,141]. Re-alignment of circadian rhythms to the natural light/dark cycle is an important health behavior that enhances resilience and adaptation to various stressors[41-43]. Additionally, a healthy brain-gut axis plays an important role in building resilience where gut microbial diversity, healthy diet and exercise can ameliorate the gut-brain axis and stress-induced cortisol release in humans and rodents. Administration of probiotics confer resilience in social defeat model and results in higher DHEA-to-corticosterone fecal metabolite[161,162], thereby mitigating the pervasive effects of early life stress on anxiety and depressive behavior as well as HPA axis activity[163].

Despite the advances in studying resilience and the multitude of contributing factors, there are still gaps in literature about genetic determinants that differentiate resilient individuals from vulnerable ones. Here we reviewed that epigenetic modification of *FKBP5* and *BDNF* genes in response to stress can be reversed by interventions to reduce stress[67,68]. Our group is currently conducting a large-scale study to determine what other genes are implicated in resilience in response to CCT psychotherapy. The advances in miRNA research can also be a powerful tool that can serve as a therapeutic target to improve resilience.

## CONCLUSION

This minireview emphasized the dynamic process of resilience and showed that it continually evolves by the intersection of different domains in human's life; nature, nurture, environment, and microbiome. Despite the large number of research studies on resilience to stress, none have established one causal factor that differentiates a resilient person from a vulnerable one. This minireview demonstrated that a holistic approach, both clinically and for research purposes, must be adopted to address the multiple elements that promote resilience and prevent physical illnesses and psychopathology. Our future direction is to further understand the role of epigenetic gene silencing in chronic stress in order to identify potential resilience genes that can be reactivated by psychotherapy and the other resilience-promoting interventions mentioned above.




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**Figure 3 Wellbeing as a measure of resilience and allostatic factors balanced output.**

## FOOTNOTES

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