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Review article: Is propionic acid a suitable model for autism?

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ABSTRACT

Autism Spectrum Disorder (ASD) is defined as different degrees of disability in social interaction, stereotyped behavior, and altered motor and sensory perception. Many scientific research are concerned with making and developing animal models of autism to figure out the appropriate correlation between behavioural changes and the pathology of brain tissue to help in clinical trials of effective therapeutic formulations. Propionic acid can be present inside the cells as metabolite in a normal state and present in high amount in the gut due to some digestive disorders or alteration in gut microbiota. Moreover, it is considered an artificial food additive. Lately, propionic acid has become a controversy model. This review assessment demonstrates a complete picture and all the available information is needed to be known about the mechanism of action of the induced autistic model. It discusses the different methods explains the pathophysiology, and various treatment modalities were tried in the propionic induced animal model. It also enlists the developmental and behavioral aspects of the model animals

Keywords

Autism spectrum disorder, propionic acid, animal model; neurobehavior.

1. INTRODUCTION

Autism is an improper term for a normal neurodevelopment disorder that is highly marked by impaired social interaction with no purpose, repeated actions like stereotype behavior. The epidemiology of autism has increased so fast recently. that it is a risk factor in the face of researchers, So, developing and improving animal model of autism is highly demanding lately. 1 in 160 children have an Autism Spectrum disorder (ASD) worldwide, and it is expected to increase globally [1]. There is evidence to suggests strong genetic and environmental factors raise the occurrence of ASD in childhood [2]. To date, there are no efficient therapeutic interventions that target the core symptoms of ASD [3,4].

Animal models were designed to mimic and study the pathological mechanisms behind the behavioural disabilities and trying to find a solution to this disorder. There are two main types of animal models: the chemical and genetic models. Environmental animal models are produced by destruction of

certain central nervous system areas by inflammations, chemical compounds, or infections. The chemical model is only effective if the used chemicals will produce the same effects in humans.

Propionic acid is a short chain fatty acid that mediated neurochemical autism and found in a high amount in blood, urine, faces samples of autistic patients [5,6] which are produced normally as a by-product in carbohydrates and some sugars metabolism. It is also found naturally in a lot of food. In addition, it has been shown to play broad roles in host cellular physiology in health and disease. The propionic acid has a critical role in the metabolism, development, and immunity in health condition, however in some inherited and acquired diseases, it affects brain function and behaviour [7-9]. As a weak acid, propionic acid is absorbed passively in the gut, liver, and brain, is uptakes systematically, both passively and actively via mono-carboxylate transporters and activates G-protein coupled receptors [7]. High levels of propionic acid are accompanied by developmental delay, oxidative stress and metabolic or immune disturbances, which have some similarities with propionic acidemia and autism [8, 6]. Within the guts of ASD patients, a high concentration of bacteria like *Bacteroidetes*, *Clostridia* or *Desulfovibrio* (all type of bacteria, which generate propionic acid)) are frequently present. Additionally, propionic acid is commonly added to processed carbohydrate containing foods that many ASD children use [10] which, additionally to gastric absorption, further increase the extra production of this acid in the gut microbiome [7].

2. MAIN CHARACTERISTICS TO ANIMAL MODEL OF AUTISM

Animal models are a very important tool used in the scientific research fields to test a new experimental science or hypothesis that is hard to perform on human [11]. The validity of animal models has been determined by (a) Construct validity, (b) Face validity, and (c) Predictive validity [12]. Although the explanation of these criteria varies [13] the main goal for animal models of ASD is high construct validity. Despite detecting ASD according to the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) set two main behavioural cores for ASD diagnosis (1) deficiency in social interaction and communication and (2) repeated without purposed movement (stereotype) [14]. But there are a lot of other features associated with ASD and could be induced in animal model. Those features like sleep problems, anxiety, neophobia (afraid to change routine), over-sensitivity to pain, seizures, the eye blink and altering senso-motor gating have also been stimulated in some of animal models. Moreover, the neurochemical alteration is stimulated to mimic those biochemical change present in ASD patient. Consequently, activate the central and peripheral immune systems [15].

Several methods and techniques are followed to establish autistic models starting from some environmental risk factors, direct injection, viral infection, and inflammation to maternal and end up manipulating a single or sets of genes. Even if a variety and numbers of technique are available, the issue is not as easy as it appears. There are many obstacles and difficulties in the way to developing new autistic models. Autism is mainly defined and considered as a group to alteration in behaviour rather than biochemical change [16]. Many complicated genes are implicated in the ASD [17]. Also, a lot of features and symptoms are associated with ASD worsen it [18]. Still, no features are present in the model to distinguish the autistic model from other neurodisorder models like schizophrenia [19]. However, animal models could not give in all cases accurate steps to similar mechanism in humans. Animal models can give good feedback on the process of brain development and help to study behavior with further look in the cell and neural circuit function then brain network activity [18]. A standardized behaviour tests have been followed to evaluate different aspects of repetitive behaviors social behavior and communication of an animal in experimental settings [12,20]. Those tests are mainly used for ASD research and models due to high demand for interpretation complex social behaviours [21].

3. PROPIONIC ACID (PPA):

The different names and symbols used for propionic acid are methyl acetic acid, propanoic acid, propionic acid, ethyl formic acid, ethane carboxylic acid, and E280 food additive. Propionic acid is artificially

prepared for industrial purposes such as food processing. It has many properties that help in mediate these processes. Anti-bacterial property makes it the best choice usage as food additive, preserves animal feed, grains, and warping food to keep it for long time. It also uses to make flavouring agent that added to food. Another important property that makes it used in many baked goods and cheese is anti-mould property. The most abundant salts of propionic acid are sodium propionate and calcium propionate. Propionic acid serves as based unit in a chemical for many manufactured products like pharmaceuticals, herbicides, dyes, textile and PPA serves as the basis of a chemical for many manufactured products. Like pharmaceuticals, herbicides, dyes, textiles, plastic products, rubber, plasticizers, cosmetics, and perfumes. It is found naturally in dairy goods and is one of the living organisms' metabolism components. Propionic acid is also produced from the breakdown of peptides and the oxidation of fat. Propionic acid is found in tiny amounts surrounding us in the environment, resulting from burned wood and produced by certain Bacteri [10, 22, 23].

4. PROPIONIC ACID TOXICITY

As a nourishment preservative, propionic acid is categorized as "Generally Safe" by the Food and Drug Administration as an antibacterial agent and additive agent. While eye direct connection with concentrated propionic acid may lead to severe inflammation, with corneal insults possibly leading to total blindness. Propionic acid is classified as destructive to dermatology tissue. Direct contact may lead to burns, pain that will turn into tissue damage with local redness [24]. Depending on time, exposure to the organ is unlikely to cause absorption of harmful doses. Inhalation may cause inflammation of the nasal tract. Propionic acid showed systemic toxicity when it was swallowed. High propionic acid amounts are also found in certain pathological states, like gingival inflammation and propionic acidemia [24-26].

Previous research has designed animal models that have specific characteristics and as an environmental factor in the development of ASD. The investigated drugs were valproic acid [27], lipopolysaccharide [28,29], and propionic acid [5,30-34, 35-37]. Researchers have studied and developed this model of short-chain acid because they have found it is elevated in autistic children's blood, urine, and feces [5,6]. They found a strong link between acidemia (increased propionic acid in plasma) accompanied by social defects. Using propionic acid as a food preservative and additive to colorful food makes propionic acid a hot issue for research [38].

5. SIMILARITIES BETWEEN PPA AND ASD SYMPTOMS

5.1 Biochemical similarities

a. Monoamines:

NE major function is adapting to environmental change, enhance flexibility and respond to emergent situation important in learning process [39]. A study had 18 adults ASD revealed alternation in NE level when compared to healthy one [40]. DA is inhibitory expiatory catecholamine. Its main function is regulating rewarding circuit that would be inhibited in autistic patient due to lack of communication. In addition, it is managing movement system [41, 42]. Previous investigations proposed that ASD could be caused by dopaminergic dysfunction specially DA imbalance in specific brain area. A hypothesis suggest alternation through meso-cortico-limbic circuit lead to social deficit and dysfunction in nigrostriatal circuit cause stereotyped behaviour dopamine receptor blocker to treat ASD repetitive behaviour [43]. Serotonin is a signalling molecule cross the body that mainly plays a role in cell development generally [39], and especially in neurons including proliferation, differentiation, migration, apoptosis synaptogenesis, neuronal and glial development. Alternation in serotonin distribution is linked to neurodevelopmental disorder like ASD [44, 45]. Many studies have been illustrated imbalance in serotonin level and its transporter in autistic children specially in the early stage of brain development as compared to healthy one [43,46]. A study to fifteen ASD adults showed lower 5-HT availability in the brain stem, total gray matter and 9 of 18 examined sub-regions of gray matter [47].

b. Gamma Aminobutyric Acid (GABA) and glutamate:

Gamma aminobutyric acid is obtained from glutamate by the action of glutamate decarboxylase, and it has a complex and homeostatic relationship balancing neuronal excitability. Glutamate represents the main excitatory neurotransmitter during brain development and it influences proliferation, migration, synapse maturation, differentiation, and cell death [48]. Many recent studies have been showed imbalance between glutamate and GABA [49-52]. A study has revealed a decrease in glutamate concentration in ASD patient in comparison with healthy adults [53]. The plasma GABA and glutamate concentration are changed in autistic children. Plasma GABA and the glutamate/glutamine ratio are increased. However, the plasma of glutamine and glutamate/GABA ratios are significantly lower when compared to the healthy one [54]. Propionic acid model showed alteration in glutamate and GABA When compared to control [55, 56].

c. Acetylcholine:

Acetylcholine is the synapse neurotransmitter utilized by engine neurons at the neuromuscular intersection. In Addition to its role in the principal synapse of the parasympathetic sensory system, it goes about as a synapse and a neuromodulator in the CNS. The principal proof of cholinergic framework irregularities in ASD has incorporated a significant decrease of nicotinic α4 β2 subtype of ACh receptors (nAChRs) in the parietal and cerebrum recognized in after death mind tests [57]. Another examination showed a decrease of cerebellar α4 nAChRs which could be connected to the deficiency of Purkinje cells and to a compensatory expansion in α7 nAChRs [58]. A few investigations on ASD models revealed the inclusion of nAChRs in regulating social and redundant practices. Propionic acid model showed alteration in acetylcholine level when compared to the control [30].

5.2. Oxidative stress:

Many studies and analysis result at autistic children patients referred to highly presence of oxidative stress markers in blood samples. According to [59], eighty-seven studies to 4928 autistic children and 4181 healthy control one. Analysis revealed that blood concentrations of nitric oxide, oxidative glutathione (GSSG), S- adenosyl homocysteine, copper homocysteine, and malondialdehyde, were higher in children with ASD than that of healthy control children. Contrary, total glutathione (tGSH), blood reduced glutathione (GSH), GSH/GSSG, tGSH/GSSG, methionine, cysteine, vitamin B9, vitamin D, vitamin B12, vitamin E, S-adenosyl methionine/S-adenosyl homocysteine, and calcium levels were remarkably reduced in autistic children when compared to healthy control children. All these results and facts make oxidative stress markers as main clue to the pathophysiology of autism [60-63]. The previous work showed activities in oxidative stress marker in brain homogenate which revealed increase in lipid peroxidation and protein carbonyl and glutathione S-transferase activity accompanied by decline in glutathione and glutathione peroxidase activity in propionic acid treatment as model of autism [7]. Consequently, previous works [35, 64, 65, 66] approved that propionic acid can lead to the same oxidative stress steps as what happen in autistic patient.

5.3. Neuroinflammation:

Neuroinflammation and cytokines are a pathological feature to autism [67]. Autistic patient samples of blood, cerebrospinal fluid and brain showed a high increase concentration of cytokines specially interferon-γ (IFN-γ), interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) when compared to healthy one [68]. Which believe to be responsible for behaviour symptoms in ASD [69]. Propionic acid elevates the levels of cytokines TNF-α, IL-6, IFN-γ, il 1β in the brain homogenate tissue [7, 35, 66 ,70,71, 72].

5.4. Mitochondrial dysfunction:

The mitochondria dysfunction (MD) is a metabolic disorder confirmed by many research and clinical investigations to individuals with ASD. That is considered MD as a medical condition associated with it[73-75]. Mitochondria is a powerhouse that provided cell with ATP, especially those have highly demand to energy like neurons. Any disturbance in neurons function will directly affect the production of ATP. So, measuring cellular bioenergetics (ATP, ADP, and AMP) can be a biomarker for mitochondria disorder [76]. Propionic acid creates oxidative stress in PC12 that leads to mitochondria malfunction and can cause shutdown of citric acid cycle [77,78]. Our previous work we measured ATP, ADP, and AMP in the brain homogenate and a significant decline in bioenergetics was confirmed when compared to the control one [79].

5.5. Behavior similarities

The most characterized phenotype to children diagnosed to be autistic mainly deficit in social communication with no developing in language and stereotype behaviour and different range of disabilities to movement according to the DSM-5 [80]. In the last 15 years, many behaviour tests were performed to evaluate propionic acid model features. The surprised one was social impairment to treated rats with each other and strangers [35, 37, 71, 81, 79, 66]. Movement disorder specially stereotype behaviour, repetitive without proposed pattern. Propionic acid treated rats showed hyperactivity in ICV [7, 81] method. While less locomotion results hypoactivity was observed by using ICV technique [82] and other methods [26, 35-37, 79, 83]. Another study found no significant change in locomotion activity[10]. While propionic acid showed less exploration [5,67], cognition impairment [71,67], place avoidance [26,36], repetitive behaviour [35,84], rearing and anxiety [35,67] and hyposensitivity.

6. ROUTE OF ADMINISTRATION OF PPA TO INDUCE ANIMAL MODEL OF AUTISM

The researchers used different types of administrations as shown in the table (1), intracerebroventricular (ICV) [7,70,71,81, ,82,8586,87], orally [30,31,35,88,84,64,66], subcutaneously [5], intraperitoneally [26,36,37 ,79,89,90], or prenatal subcutaneously [32-34,83]. Earlier study Started the model of propionic acid through ICV tested many doses [7]. They found effective dose was a high dose for adult male Long–Evans 300 to 350 g (approximately 75day) by two experiment ways dose once daily for 13 consecutive day and twice daily for 7 days induced behaviour and patho-histology implications. Also, yielded male wister rat pups 250 mg/kg orally for three days [30]. Whereas male Sprague–Dawley rats weighing 80–100 g have been injected by propionic acid 500 mg/kg once a day subcutaneously for five days[5]. In addition injected Wister rats weighing 115–125 g, a single dose of propionic acid(175 mg/kg, ip) for ultrastructure examination to amygdala and hippocampus [89,90]. Moreover, Wistar rats pups weighing 45–60g have been injected once daily 250 mg/kg ip for 17 consecutive days [79]. All these previous studies tried to produce an ASD animal model to get its research demand.

7. BEHAVIOR TESTS USED IN THE EVALUATION OF PPA MODEL

MacFabe *et al* used open field in ICV model to evaluate locomotors activity in propionic acid treated rat and he found increase in entire distance moved in comparison with control [7]. Circular open field arena was used by [81,85] to measure movement activity and social interaction to propionic acid rat then by analysing different criteria. They found hyperactivity with social interaction impairment. As well as water maze and beam task performed on propionic acid treated rat. Results indicated that propionic acid caused cognition impairment and senso-motor deficit. Further tests were done by [71] three tasks: first one was object direct behaviour, ICV propionic acid rat did not interact with three objects but preferred interaction with one that reflected intellectual impairment. Second one was a novel rat vs novel body duration with novel rat decreased in comparison with control. Third one was T maze that confirmed cognition impairment.

Intraperitoneal injection (ip) of propionic acid to adult female rats 500 mg/kg for five days did not show significantly change in locomotor or social interaction when compared to control [10]. However, another study gave propionic acid ip to male rats 500 mg/kg for five days [5], they showed a decrease in explorer activity to propionic acid treated rat in comparison with control and there was a decline in time spent to approaching rat comparing to vehicle in open field maze. Moreover, researchers tested propionic acid ip treated rats in open field [37]. They revealed that propionic acid treated rats showed less locomotion and impaired in a social interaction. Also other scientists examined propionic acid ip treated rats with three box chamber and Y maze [37]. The results showed social deficit and repetitive behaviour. While other work used two doses to test Acoustic startle response they found that propionic acid treatment cause hyposensitivity in comparisons with control [36].

Table 1 showed different routes of administrations of PPA to induce animal model of autism.

Route of administration	**Time**	**Dose**	**Animal**	**Ref**
Intracerebro-ventricular **ICV**	13 days once daily	4.0µl of a 0.26 M solution	Adult male Long–Evans 300to350g	[7,70,71,81, 82,85, 86,87]
	twice daily for 7 days			
Orally	Three days	250 mg/kg	Wister albino rat pups 45-60g	[30,31,35, 64,66, 84, 88]
Prenatal	twice a day, G12–16	(500 mg/kg) Subcutaneous	female Long–Evans 230 to 305g	[32-34,83]
Subcutaneous	5 days	500 mg/kg	male Sprague–Dawley rats weighing 80–100g	[5]
Intra-peritoneal (ip)	Single injection	175mg/kg	Wistar rats, weighing 115 –125g	[89, 90]
	Once daily for 17 days	250 mg/kg	Wistar rats, weighing 45–60g	[79]
Cell line	50% confluence		PC12	[8,77,78]

Whereas, researchers have been tested orally administrated pups' model in three box chamber, Y maze, T maze and hole board apparatus [35]. They indicated that propionic acid treated rats showed reduction in social communication, repetitive behaviour, anxiety, and rearing behaviour.

Offspring belonging to mother treated with propionic acid were tested in open field and the data revealed that male pups were a less active than female. Propionic acid treated rat tested to place avoidance propionic acid rat produced a remarkable place avoidance and notable reduced locomotors activity.

Table 2 showed Behavior tests used in the evaluation of PPA model

Ref	Animal	Test	Criteria tested	Method of induction	Conclusion
[7]	Long–Evans (300 - 350g) Roughly 75 days old	Open field	Locomotor activity	twice daily ICV infusions for 7days	Expanded in entire distance traveled
[81]	Long–Evans (200 to 250g)	Circular open field arena	Mean distance separated, dark phase Closely, light stage Closely, dark stage Play behavior light phase Play behavior dark phase Whole distance travel, light stage Whole distance travel dark stage	ICV	Hyperactivity with social debilitation
[85]	Long–Evans (200 to 250g)	Water maze beam task	Spatial cognition Sensorimotor	ICV Three to five injections	PPA cause discernment debilitation, sensorimotor imperfection
[71]	Long–Evans (300-350g) Roughly 75 days old	object direct behavior	1-time in object area 2- total time into each of 3 object area 3-whole number of sniffing about body	twice daily ICV infusions for 7days twice daily	No consistency Tradition a list in collaboration with one item than others Debilitation in psychological conduct.
		Novel rat vs. novel object	- Duration spent with novel rat - Duration spent with novel object		Time spent in moving toward rodent is exceptionally decline in PPA when contrasted with vehicle with no adjustment of time went through with object. Impedance in social behavior
		T-maze	Percent of correct alternation		PPA group showed critical reduction in percent of right alternation that reflect a cognitive impairment
[33]	Pregnant Long-Evans rats	Open field	Locomotor activity	Subcutaneous once a day to pregnant female (G12- G14)	Female pups are more dynamic than male pups.
[82]	Rat	Open field	Locomotor activity		Reduce locomotion

	8-weeks-old			ICV	activity
			Social interaction		PPA induced social debilitation
[26]	Long Evans rats (200 to 300g)	Place conditioning apparatus	Place avoidance	ip (500 mg/kg) for three days	PPA produce a remarkable place avoidance and notable reduce locomotor activity
[10]	Long Evans rats (100-140 g) about 30-35 days old	Open field	repetitive, locomotor and anxiety	ip (500 mg/kg) for 5 days	PPA did not significantly alter locomotor, repetitive or anxiety-related behaviors in female adolescent rats.
[5]	Male Sprague–Dawley rats weighing 80–100g	Social interaction test	(a) following and chasing (b) adjacent interaction (c) anogenital interaction (d) head-to-head interaction	subcutaneous (500 mg/kg) once a day for five consecutive days.	PPA treated rat reduced Explore activity
		Open field test	exploratory activity		approaching numbers decline
[35]	Wister rat Pups 21 day	three box chambers	Social interaction	250 mg/kg Of PPA for three days	Reduction in social approaching
		Y maze	spatial memory , active memory, attention memory and repetitive behavior		Rats represented a repetitive behavior
		Plus, maze	Anxiety like behavior		reduced the percentage of time spent and number of entries in open arms in comparison to control rats PPA produce anxiety like behavior
		Hole board apparatus	exploratory activity		Increase, first poke, decrease the number of hole poking and rearing
[37]	Juvenile male rats 35 days	Circular open field	Paired social interaction	ip injections of buffered PPA (500 mg/kg) for 7 days	PPA impaired social interaction
		Individual locomotor activity	Locomotor activity		PPA produce hypoactivity

[36]	Long-Evans rats (250–300 g,	Startle response procedure	Acoustic Startle Response	ip low dose 250 mg/kg and high dose 500 mg/kg	PPA produce hyposensitivity
[79]	Rat pups 21 day	Three box chambers	Social interaction	Ip 250 mg/kg For 17 days	PPA induce social impairment
		Y maze	repetitive behavior		PPA reduce percent of alternation

8. SUPPLEMENTS AND ANTIOXIDANT USED TO AMELIORATE OR PREVENT THE ACTION OF PPA

Propionic acid animal model for autism is considered a new controversy model. However, many researchers have been started to test supplements like omega-3 and N-acetylcysteine [30, 91]. They treated Wister rat pups (45-60g) with orally 250mg/kg of propionic acid. Therefore, rats tested for Omega -3 (100 mg/kg) for five days as a protective dose before propionic acid treatment. The result revealed a highly protective potency to omega -3 that were recorded by increasing the whole brain 5HT, DA, GABA, and phospholipids (PE, PS and PC) and decreasing IL-6, TNF-a, and caspase-3. Another study have been used N-acetylcysteine 50mg/kg for five days before and after propionic acid treatment for three days [91]. Results showed that N-acetylcysteine can use as a protective and a therapeutic treatment because it helps in keeping and restore the normal level of glutathione and decrease urea and lipid peroxidation. In the same way, compare neurotoxicity of antibiotics against propionic acid neurotoxicity in Syrian hamster used clindamycin 30 mg/kg for three days in comparison with propionic acid, carnosine10 mg/kg/day orally for one week before treated by propionic acid in comparison with propionic acid and pre-treatment and carnitine 50 mg/kg/day orally for one week before treated by propionic acid in comparison with propionic acid group. Biomarkers were measured in Cortex and medulla. They results showed that clindamycin produces neurotoxicity, carnosine and carnitine increase brain monoamines and GABA. These supplements can provide as protective mechanism against propionic acid neurotoxicity [31]. Vitamin D is highly recommended treatment against autistic symptoms that found in countries where children did not expose to sun properly and always suffer from vit D deficiency [92]. (1000 IU/kg/day) of alpha 25 hydroxy vit D have been tested against pre and post propionic acid treatment three days orally model. The result showed that vit D has a protective effect more than therapeutic effect because in a pre-treatment it decreased neuroinflammation represent in IFγ and keep glutathione and DNA. Vit D has been recommended to pregnant as a protective strategy against autism[92]. Similarity, other workers have been used the same model to test co enzyme Q10 and melatonin (4.5, 10 mg/kg) for one-week pre and post treatment [93]. Results revealed that both have therapeutic and protective effect. Moreover, other paper used the three-day model on male Sprague Dewily rats 21 days to test bee venom (BV) (5 mg/kg) subcutaneously pre-treatment for 2 weeks and post two weeks [65]. Results showed that BV suppress apoptosis by enhancing Bcl-2 expression and caspase -3 and restore normal ultrastructure of amygdala. It can be used for protection and therapeutic against oxidative stress, DNA damage, and neural death. Moreover, other have been used the three-days orally treated propionic acid model in Wister rats in comparison with ampicillin[64]. They found that ampicillin produce neurotoxic state like propionic acid. The balanced diet could restore these neuro-toxication.

Whereas the propionic- ICV model have been used in male Sprague Dawley rats (250-280 g) 4-month-old for 11 days then treated by three curcumin doses (50,100,200 mg/kg) orally for 25 days[94]. Results indicated that curcumin could restore the symptoms associated with autism like behaviour, oxidative, nitro-stative stress, and mitochondria dysfunction by reducing TNFα. Another study used Bee pollen 50 mg

for 30 days after PPA orally treatment for three days [84]. The results revealed that Bee pollen increase monoamines and decrease IFN-γ and caspase 3. Bee pollen was effective in preventing the neurotoxic effect of PPA. Bee pollen (50 mg/kg) have been tested for 30 days after three-day propionic acid (250 mg /kg) orally model [96]. The results showed that bee pollen has ameliorating effects on glutamate excitotoxicity and the impaired glutamine-glutamate-GABA circuit as two etiological mechanisms in propionic acid-induced neurotoxicity.

Antioxidants also are tested against propionic acid like Co enzyme Q10 and melatonin [95]. Co enzyme Q (4.5 mg/kg) and melatonin (10 mg/kg) used for one week before and after treatment with propionic acid for three days. The data illustrated that coenzyme Q and melatonin were very effective in rebalancing the normal level of most of the impaired fatty acids in PPA-intoxicated rats. These data suggested that both supplements ameliorate the autistic biomarkers induced in rat pups. Diet rich protein presented by [72] as a solution to help synthesis neurotransmitters and this hypothesis experimented in three days orally model Wister rats. Data indicated that dietary protein level may be a useful tool to find out a path to restrict neurotransmitter alterations in neurodevelopmental disorders like autism. Omega -3 dose (200 mg/kg/day) for 30 days tested in Juvenile Rats (80– 120g) after treated with propionic acid. Vit B12 (16.7 mg/kg/day) treated for 30 days after propionic acid and combination of Omega-3 and Vit B12 [97], [99]. They results showed that these supplementations reduce oxidative stress and combination inhibits *clostridia* growth they suggested taking this combination as therapeutic treatment. Probiotic also used by [98] in the same model but in young golden Syrian hamsters (60 - 70g) given 0.2 g probiotic/kg for three weeks post propionic acid treatment. Results illustrated that probiotic can be to ameliorate glutamate excitotoxicity by increasing depleted GABA and Mg^{2+} and reducing the excitatory neurotransmitter, glutamate. peroxisome proliferator-activated receptor-α (Fenofibrate) [35]. Moreover, a fenofibrate (100 mg/kg and 200 mg/kg) treatment tested for 24 days to treat propionic acid toxication. The cerebellum, brain stem and prefrontal cortex were dissected and assessed for biochemical parameters. Data reflected that Fenofibrate in two doses attenuate the action of propionic acid by decreasing neuroinflammation (IL-6, IL-10 and TNF-α) and increased glutathione level. In addition, nettle leaves , roots (50 mg /kg) and risperidone (1mg /kg) tested against propionic acid ip model for 17 days in rat pups (45-60 g). The results showed that nettle leaves had poor effect on brain monoamines, bioenergetics, and behaviour improvement. While the roots showed a great effect on brain monoamines, bioenergetics, and behaviour [79]. Risperidone enhances monoamines system and behaviour.

Table 3 showed supplements and antioxidant used to ameliorate or prevent the action of PPA

Treatment	Ref	Route of administration of PPA model	Animal	Treatment period and dose	Outcomes
Omega-3	[30]	Orally 250 mg/Kg/day for 3 days	rat pups (45-60) g	100 mg/kg for five days orally before PPA treatment.	Remarkable protective effects against PPA.
N-acetylcysteine	[91]		rat pups (45-60) g	50 mg/kg orally for five days before and after PPA treatment.	Ensure against and treated PPA inebriation.
clindamycin	[31]		Syrian hamsters	30 mg/kg orogastrically for three days alone in comparison with PPA.	Produce neurotoxicity
carnosine	[31]		Syrian hamsters	10 mg/kg/day orally for one week before PPA treatment.	Enhancements to ensure against PPA neurotoxicity.

carnitine	[31]		Syrian hamsters	50 mg/kg/day orally for one week before PPA treatment.	Improvement to ensure against PPA neurotoxicity.
Vit D	[92]		Young male Wister rats (45 _60) g	1000 IU/kg/day of alpha ,25 hydroxy vit D orally - pre and post PPA treatment.	Vit D revealed an incredible defender than treatment toward PPA
Coenzyme Q	[93]		Young male Wister rats (45 _60) g	4.5 mg/kg orally for one week - pre and post PPA treatment.	Could be utilized as extra supplementation to keep away from the early neuro-disorders
Melatonin				10 mg/kg orally for one week - pre and post treatment.	
Ampicillin	[64]		Young male Wister rats (45 _60) g	50 mg/kg/day orally for three weeks- as compared to PPA.	Ampicillin produce neurotoxic express that is like PPA neuro-toxication that might be reestablish by adjusted eating regimen.
Curcumin	[94]	4 µl ICV	Male Sprague Dewily rats (250-280) gm 4-month-old	50,100,200 mg/kg/day orally for 25 days - post PPA treatment	Curcumin can restore the feature accompanied with autism like oxidative, nitro-stative stress, mitochondria dysfunction reduces TNFα
Apitoxin (bee venom)	[65]	Orally 250 mg/Kg/day for 3 days	Male Sprague Dewily rats 21 days	0.5 mg/kg subcutaneously Pre for 2 weeks and pre and post for 2 weeks PPA treatment.	BV stifle apoptosis by upgrading Bcl-2 articulation and caspase - 3 reestablish ordinary ultrastructure of amygdala and cand give as defensive and restorative against Oxidative pressure and DNA harm, neural passing.
Bee pollen	[84]		rat pups (45-60) g	50 mg bee pollen orally for 30 days after PPA treatment.	Give calming and hostile to apoptotic impacts against PPA inebriated rodents.

Q 10	[95]		rat pups (45-60) g	4.5 mg/kg orally for one week before and after PPA treatment.	Elevated the level of all unsaturated fatty acid so help in protect and therapeutic against PPA
Melatonin	[95]		rat pups (45-60) g	10 mg/kg orally for one week before and after PPA treatment.	decline the level of all unsaturated fat help in protect and restorative against PPA.
Diet rich protein	[72]		rat pups (45-60) gm	Diet rich protein	dietary protein level may be valuable Technique to figure out a way to limit neurotransmitter alterations in neurodevelopmental diseases like autism.
Bee pollen	[96]	Orally 250 mg/Kg/day for 3 days and 75 mg/kg for 10 days	young male Western rats 3–4 weeks of age, and 45–60 g	50 mg/kg orally for 30 days	improving impacts on glutamate excitotoxicity and the disabled glutamine-glutamate-GABA circuit as two etiological components in PPA-initiated neurotoxicity.
Vit B12	[100]	Review			Suggest use B12 against PPA model
Omega-3	[97], [99]	Orally 250 mg/kg/day for 3 days	Juvenile Rats (80–120g)	dose of 200 mg/kg/day orally for 30 days after PPA treatment.	Reduce oxidative stress.
Vit B12	[97], [99]		Juvenile Rats (80–120g	(16.7 mg/kg/day) orally for 30 days after treated with PPA	Reduce oxidative stress.
Omega -3 and vit B12	[88],[99]		Juvenile Rats (80–120g	dose of 200 mg/kg and 16.7 mg/kg/day) orally for 30 days after PPA treatment.	supplementation with Omega-3 and nutrient B12 can bring about a positive restorative impact by hindering *Clostridia* growth.

Probiotic	[98]		young golden Syrian hamsters weighing between 60 and 70 g	0.2 g probiotic/kg orally for three weeks – post PPA treatment	probiotics can be improving glutamate excitotoxicity by elevating depleted GABA and Mg2+ and decreasing the excitatory neurotransmitters, glutamate.
peroxisome proliferator-activated receptor-α (Fenofibrate)	[35]		Wister rat pups from 21 day	Fenofibrate (100 mg/kg and 200 mg/kg) orally for 24 days - pretreatment	attenuated PPA-induced oxidative stress and neuroinflammation.
A selective peroxisome proliferator-activated receptor-γ (pioglitazone)	[66]		Wister Rat pups from 21 day	10 mg/kg and 20mg/kg Orally For 27 days-pretreatment	Pioglitazone attenuate behavior defect, oxidative stress and neuroinflammation produced by PPA.
solanesol	[103]	ICV injection (4µl/0.26M)	Wistar rats (250-300 g), aged 4-6 months	40 and 60mg/kg Ip For 33 days – pretreatment	Combination enhancing the cognitive deficits, reducing the level of inflammatory mediators and oxidative stress.
Aripiprazole Citalopram Memantine Donepezil				5,10,5,3mg/kg IP respectively, for 33 days – pretreatment	
Lactobacillus paracaseii and Protoxin	[101] [102]	Orally 250 mg/kg/day for 3 days	Hamsters	dose of 250 mg/kg/day orally for 28 days-pretreatment.	Enhance neuroinflammation and dysbiosis produced by propionic acid.
propolis and bee pollen				dose of 250 mg/kg/day for 28 days – pretreatment.	
Oxiracetam	[104]		Male Wistar rats (45–60g) with 3week aged	25,50 mg/kg ip For 7 days – post treatment.	Oxiracetam alone and in mix with zinc managed the cost of predominance medically introverted impact through cell reinforcement, mitigating and against excitotoxic systems and could fill in as appealing technique in overseeing mental imbalance.
Oxiracetam And zinc				25 oxiracem ip and 4 mg/kg po For 7 days – post treatment	
Zinc				4 mg/kg po for 7days post-treatment	
Risperidone				1 mg/kg ip for 7 days post-treatment.	

Nettle (leaves)	[79]	ip 250 mg/Kg/day for 17 days	Rat pups (45-60) g	50 mg/kg orally for 17 days after treated by PPA	Showed neuro toxicity
Nettle (root)	[79]	i.p250 mg/Kg body weight/day for 17 days	Rat pups (45-60) g	50 mg/kg orally for 17 days after PPA treatment.	Improve behavior, monoamine system and bioenergetics
Risperidone	[79]	Ip 250 mg/Kg/day for 17 days	Rat pups (45-60) g	1 mg/kg orally for 17 days after treated by PPA	Improve behavior, monoamine system and bioenergetics

9. **CONCULSION**

Propionic acid model demonstrates many common features with autistic children starting from the internal neurochemistry inside each cell. Increasing the oxidative stress and free radicals in propionic model induced mitochondrial dysfunction that emit intense cytokines to irritate and altered different neurotransmitters. Moreover, the gastrointestinal abnormalities and patho-histological similarity were reported between the propionic model and ASD patients. Using appropriate behaviour tests and applied criteria of the modelling showed that propionic acid according to Crawley [12, 20] could fulfil more than three aspects. Propionic acid -ICV model provides the hardest condition to modelling nervous system diseases. These ICV model could infect specific brain area to make the closest one to the autism and distinguished it. Whereas the propionic acid -IP model and the other methods are still accepted because it offers the same pathophysiology and the symptoms of ASD behaviour. It also considered as a cheap and easy way to test new therapeutics providing an adequate main requirement.

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