ISSN NO: 2771-8840
Date of Publication: 04-09-2022

Interaction of p-glycoprotein inhibitor-Verapamil- and Colchicine on some Neurobehavioral and Biochemical parameters in mice

Tayseer Shaker Mahmood [1] , Raghdaa Dawood Obaid [2] , Duraid Abdul-Hadi Abass [3]
[1] ·Al-Hadi University College \ Nursing Department , Iraq
[2] ·Al-Hadi University College \ Nursing Department , Iraq
[3]·University of Baghdad\Veterinary medicine collage\ Department of Physiology, Biochemistry & Pharmacology, Iraq
tayseershakermahmood@gmail.com

Abstract: Neurobehavioral methods were used to investigate the effect of co-administration p-glycoprotein inhibitor –verapamil- on colchicine –p-glycoprotein substrate given alone and in combination at low and high therapeutic oral doses given daily for 3 months in (63) albino mice allocated to (7) equal groups as following: colchicine low and high dose groups (50µg ,70µg\kg\b.w) respectively , verapamil low and high dose groups(1.5 mg ,3mg\kg\b.w) , combined colchicine &verapamil in low doses and high dose groups (50µg+1.5mg , 70µg+3mg\kg\b.w) compared to control one given distilled water.The results of open field methods ,negative geotaxis, head pocking, cleft avoidance, swimming rank and Y-maze methods indicated that both drugs at low and high dose alone and in combination shown mostly significant change in the results at dose dependent manner specially for combined one .Different dosing regimen resulted in significant changes in cognitive ,locomtor activity ,short memory, mental and peripheral activity for all tested groups specially in single higher and combined dosed groups, also significant increase in actylcholinesterase (AchE) activity at 45 days for verapamil high dose group and in combined verapamil & colchicine low and high dosed groups while at 90 days show decrease in AchE activity were recorded for all treated groups compared with control one. While creatinine kinase levels were only recorded significant decrease in combined dosing groups at 45 days with much higher inhibition at 90 days compared to lesser inhibition in verapamil and higher colchicine dosing groups as indicative of muscular activity changes.

Keywords: AchE activity , Creatinine kinase , neurobehavioral , p-glycoprotein , toxic effect.

Article highlights: To investigate the toxicity effect of p-glycoprotein interaction **.**

Introduction: P-glycoprotein (P-gp), the permeability glycoprotein or plasma glycoprotein is an active, efflux, membrane bound transport protein pump **(1)**. P-gp is a member of ATP binding cassette (ABC)super family, multidrug resistance (MDR)/transporter associated with antigen processing (TAP), sub-family B ,and member 1, abbreviated as ABCB1. P-gp can be viewed as a unique defensive barrier network against the entry of xenobiotics into the body. This efflux carrier decreases the bioavailability of administered drugs by preventing their sufficient accumulation intracellularly the efficacy of drugs is lowered. It also alters the pharmacokinetics and pharmacodynamics of its substrates **(2).**
Neurobehavioral testing as a subclinical observation in neurotoxicity
Neurobehavioral assessment of outcome has played an integral part in neurotoxicity research. The purpose of this test is to evaluate several, commonly used neurobehavioral measures along the dimensions of reliability, sensitivity, and validity. Open field test used to evaluate the general locomotors activity, exploration, rearing, and also include the frequency of defecation and urination **(3).**Negative geotaxis test evaluates the motor activity of animals **(4).** The Cleft avoidance test evaluates the normal behavior during the risk condition and detecting the normal reflexes of the animals **(5) .** The Head pocking test use to determine the degree of cognitive function of animals and exploration of environment **(6).** The Swimming rank test use to reflects the integration of the brain function **(7). Finally,** Y – maze test use to reflects the state of short memory of the animals **(8, 9).** Motor activity is usually quantified as the frequency of

ISSN NO: 2771-8840
Date of Publication: 04-09-2022

movements over time. Effects of chemicals on motor activity are usually expressed as total number of counts or as a percentage of some control value (i.e., control group or pre-exposure baseline). The frequency of motor activity within a test session usually decreases, a phenomenon known as habituation. One major conclusion from motor activity is that the acute effect of most drugs is a depression of motor activity and that the hyperactivity may be evidence of a specific effect on the nervous system **(9).**

Neurobehavioral changes may also influence the Ach activity in the brain. Ach in the brain alter neuronal exitability, influence synaptic transmission, induced synaptic plasticity and coordination the firing of group of neuron. These action affect the synaptic properties of neuron in several brain areas and discuss the consequence of this signaling on behavior related to drug abuse. The co-administration of a P-glycoprotein inhibitor causes a much greater increase in drug concentration in brain than in plasma. A major problem that may confound attempts to use P-glycoprotein modulators in the clinical setting. P-glycoprotein-mediated drug interactions may be anticipated when P-glycoprotein substrates and P-glycoprotein inhibitors (or inducers) are co-administered. Inhibition and induction of P-glycoprotein in animals and humans have been reported **(10).**

Materials and methods:

In this experiment ,colchicine 1 mg and verapamil 40 mg tablet were used to prepare the concentration (50µg\ml and 70µg/ml for low and high dose for colchicine , 1.5 mg\ml and 3mg\ml for low and high dose for verapamil)according to body weight of the animals ,also using stomach tube for oral administration , EDTA tube for blood samples for measuring AchE levels, and non EDTA tube for serum measuring creatinine kinase levels , PH meter ,spectrophotometer, creatinine kinase kit and hand made neurobehavioral apparatus.

Sixty three Adult Webster Albino mice obtained from Al-Razi center\ Baghdad , aged over 3 months and weighted 25-30 gram were used to perform different studies . They were fed standard pellet diet and drink tap water. The animals were left in special cages with normal conditions two week for adaptation in the animal house in veterinary medicine \university of Baghdad. Thirty animals for acute study while sixty three were used in chronic study. **This study was performed under the rules of ethics for management laboratory animals submitted by university of Baghdad and supervised by sided committee in the college of veterinary medicine.**

Methods: The neurobehavioral test done by using neurobehavioral apparatus , AchE test was done by using (Michel method) which is based on the change of PH of media by using (PH meter) and by measuring the percentage of inhibition of AchE by using the following equation **(11).** :

$$\text{Cholinesterase inhibition\%} = \frac{\Delta\text{PH of Experimental time period} - \Delta\text{PH at zero time period}}{\Delta\text{PH at Zero time period}} * 100$$

Total CK level measuring involves spectrophotometric in a wave length 492 nm (490-510) determination of the rate of the foregoing reaction using CK kit. The experimental groups divided into Colchicine low and high therapeutic dose (CL&CH) of (50 &70µg\ kg.b.w) respectively and Verapamil low and high therapeutic dose (VL&VH) of (1.5 & 3 mg \kg.b.w) respectively , Combined doses groups of both drugs at low doses (CVL) at (50µg+1.5mg \kg.b.w) and high doses (CVH) at (70µg+3mg \ kg.b.w) for colchicine and verapamil respectively. The seventh group was considered as control negative dosed daily with distilled water.

Results:

1. Neurobehavioral study: Open field test is the test that evaluate the general locomotors activity, exploration, rearing, and also include the frequency of defecation and urination. The results of open field test within groups showed significant decrease in 90 days as compared with 45 days. At 45 days of treatment, the results between groups showed significant decrease in CH and CL in dose and period dependent manner as compared with control group except the VH showed higher significant effect as compared with all other

ISSN NO: 2771-8840
Date of Publication: 04-09-2022

groups and control one but VL and VH showed higher decrease at 90 days of treatment as compared with control while combined doses showed no effect .

Negative geotaxis test that evaluate the motor activity of animals and cleft avoidance test that used for evaluate the normal behavior during the danger condition and detect the normal reflexes showed higher effect after 90 days for test groups specially for VL and VH for negative geotaxis and nearly same differences results for colchicine as compared with control while the combined dosing group showed less effect but still significantly different with control one.

Head pocking test that was used to determine the degree of cognitive function of animals the results showed higher effect in all groups at 45 days ,the higher effect showed in CH group , the significant decrease effect at 90 days showed in the combined dosing groups in dose dependent manner as compared with control one **(4.8 ± 0.66, 3.2 ± 0.37, 10.8 ± 0.58) respectively.**

The swimming rank results showed significant changes in grade of the test in the colchicine groups in a dose dependent manner at 45 and 90 days, the significant effect of combined dosing animals showed only at 90 days that recorded grade 3 of the test.

Y-maze test used to reflect the state of short memory of animals, the higher effect showed in the colchicine and verapamil alone groups at 45 and 90 days but no significant effect in the combined dosing groups, table (1).

2. AchE activity: At 45 days of different drugs dosing , the result of AchE activity showed highest percent significant increase ($p \leq 0.05$) recorded especially in CVH , CVL ,and VH, while at 90 days dosing all treated groups recorded significant decrease ($p \leq 0.05$) in ΔPH of AchE as compared with control one ,and no significant differences between each other, table(2).

3. Creatinine kinase levels: The results of (CK) test between groups after 45 days treatment showed significant decrease($p \leq 0.05$) in combined dosing groups (CVH and CVL), At 90 days treatment serum CK level recorded highly decrease in combined dosing groups as compared with control , table (3).

Table (1) neurobehavioral tests (open field, negative geotaxis,cleft avoidance, head pockind, swimming rank and Y-maze tests after chronic administration of colchicine and verapamil as alone and combined different doses in mice.

Open field\cross no.\3 min				Negative geotaxis\3minute			Cleft avoidance\3minute		
Period / G	Zero time	45 days	90 days	Zero time	45days	90 days	Zero time	45days	90 days
Control	93.55 ± 2.12 Aa	95.71 ± 2.02 A a	97 ± 2.42 A a	2.33 ± 0.28 A a	2.14 ± 0.26 B a	2 ± 0.31 D a	1.66 ± 0.23 A a	1.71 ± 0.28 C a	1.4 ± 0.24 D a
CL	83 ± 4.65 Ba	75.71 ± 5.37 C b	53.4 ± 6.32 D c	2.66 ± 0.23 A c	3.85 ± 0.40 A b	9.4± 0.81 B a	2 ± 0.29 A c	3.57 ± 0.38 B b	5.8 ± 0.37 AB a
CH	87.66 ± 4.85 Ba	78.57 ± 4.5 BC ab	71.4 ± 4.65 C b	2.44 ± 0.17 A b	2.71 ± 0.42 B b	6.2 ±0.58 C a	1.77 ± 0.28 A c	3.1 ±0.22 B b	6.61 ± 0.42 A a
VL	88 ± 4.89 Ba	71.28 ± 2.98 C b	56.6 ± 3.35 D c	2.66 ± 0.23 A b	2 ± 0.30 B b	10.8 ± 0.96 A a	1.89 ± 0.26 A c	2.85 ± 0.26 B b	5.22 ± 0.58 B a

ISSN NO: 2771-8840
Date of Publication: 04-09-2022

VH	99.88 ±2.52 Aa	108.85 ± 6.58 A a	64 ± 5.47 C b	2.66 ±0.33 A b	1.71 ± 0.28 BCb	11 ± 0.54 A a	1.45 ± 0.18 A c	3.42 ± 0.38 AB b	6.62 ± 0.51 A a
CVL	94.44 ± 3.55 Aa	87.42 ± 6.29 B b	86.2 ± 4.97 B b	2.33 ± 0.28 A b	2.57 ± 0.20 B b	8.4 ± 0.67 B a	1.89 ± 0.26 A b	4.14 ± 0.34 A a	4 ± 0.32 C a
CVH	90.77 ±4.03 A ab	85.14 ± 3.69 B b	99.6 ± 3.44 A a	2.44 ± 0.29 A b	3.28 ± 0.28 A b	6.2 ± 0.86 C a	1.78 ± 0.28 A b	3.71 ± 0.28 AB a	3.41 ± 0.24 C a
	LSD=9.43			LSD=1.03			LSD=0.86		

	Head pocking\3minute			Swimming rank\20second			Y-maze\12 trails		
Period / G	Zero time	45 days	90 days	Zero time	45 days	90 days	Zero time	45 days	90 days
Control	10.33 ± 0.4 A a	10.71 ± 0.42 A a	10.8 ± 0.58 A a	Grade 4 9 of 9	Grade 4 7 of 7	Grade 4 7 of 7	64.44 ± 2.94 A a	65.71 ± 3.69 A a	66 ±5.09 AB a
CL	10.66 ±0.55 A a	6.85 ± 0.82 B b	7.8 ± 1.06 B b	Grade 4 9 of 9	Grade 3 1 of 7	Grade 3 2 of 7	64.44 ± 2.77 A a	37.14 ± 2.86 C b	44 ± 4.1 B b
CH	10.33 ± 0.5 A a	7.71 ± 0.86 B b	3.8 ± 0.37 C c	Grade 4 9 of 9	Grade 3 1 of 7	Grade 3 1 of 5	72.22 ± 4.34 A a	35.71 ± 2.02 C b	44.2 ±2.45 B b
VL	10.77 ±0.68 A a	7.51 ± 0.36 B b	6.2 ± 0.58 B b	Grade 4 9 of 9	Grade 4 7 of 7	Grade 4 7 of 7	67.78 ± 5.21 A a	50 ± 4.36 B b	54.2 ±4.2 B b
VH	10.22 ±0.46 Aa	10 ± 0.89 A a	5.6 ± 0.6 BCb	Grade 4 9 of 9	Grade 4 7 of 7	Grade 4 7 of 7	70 ± 5.53 A a	52.85 ± 1.84 B b	54±5.09 B b
CVL	10.33 ±0.52 A a	5.28 ± 0.64 B b	4.8 ± 0.66 C b	Grade 4 9 of 9	Grade 4 7 of 7	Grade 3 1 of 5	65.55 ±3.76 A a	58.57 ± 2.61 AB a	56 ± 5.04 B a
CVH	8.11 ± 0.45 Aa	5.85 ± 0.45 B b	3.2 ± 0.37 C b	Grade 4 9 of 9	Grade 4 7 of 7	Grade 3 1 of 5	63.33 ± 4.71 A a	64.28 ±2.98 A a	68 ± 3.74 A a

ISSN NO: 2771-8840
Date of Publication: 04-09-2022

	LSD=2.96				LSD=11.13

Table (2)Percentage of plasma AchE activity % after chronic administration of colchicine and verapamil as alone and combined different doses in mice treated groups compared with control

Period / G	45 day	90 day
CL	43.4 ±3.13 C b	76.2 ±2.8 A a
CH	78.4 ±6.65 B a	86.4 ±1.5 A a
VL	84.2 ±7.56 B a	69.2 ±1.77 A b

ISSN NO: 2771-8840
Date of Publication: 04-09-2022

VH	138.2 ±15.21 A a	70 ±2.44 A b
CVL	133.2 ±8.42 A a	92.4 ±1.28 A b
CVH	139.5 ±10.13 A a	79 ±3.78 A b
LSD=24.93		

Table (3) serum Creatinine kinase (CK) mg\dl test after chronic administration of colchicine and verapamil as alone and combined different doses in mice.

,

Period / Group	45 day	90 day
Control	0.73±0.1 BC a	0.81±0.02 A a
CL	0.86±0.01 A a	0.88±0.04 A a
CH	0.82±0.01 AB a	0.55±0.04 BC a
VL	0.82±0.02 AB a	0.61±0.05 B b
VH	0.76±0.01 BC a	0.45±0.03 C b
CVL	0.68±0.007 C a	0.36±0.02 D b
CVH	0.65±0.009 C a	0.24±0.01 E b
LSD=0.128		

N=7 **,**

CL: colchicine low dose (50µg\kg) , CH: colchicine high dose (70µg\kg), VL:verapamil low dose (1.5mg\kg) ,VH: verapamil high dose (3mg\kg) ,CVL: colchicine - verapamil low dose (50µg\kg , 1.5mg\kg) ,CVH: colchicine - verapamil high dose (70µg\kg , 3mg\kg) capital letters donate differences between groups p≤0.05 ,small letters donate differences within groups p≤0.05.

Discussion:

The results of neurobehavioral test were exclusive with fluctuated effect for verapamil and colchicine after alone and combined dosing in mice that manifested change in locomotor activity, exploration, memory, cognitive and integration of brain function for different dosing groups. These results were attributed to the change in concentration of the two drugs both centrally in brain and peripherally at neuromuscular synapse possibly due to the inhibiting effect of verapamil on brain p-glycoprotein that affect transport and deposition of colchicine as substrate as well as verapamil itself in brain with consequence effect on their concentration in plasma and neuromuscular synapse , also both drugs verapamil and colchicine cause change in neurotransmitters level both centrally and peripherally, so giving both drugs at a high therapeutic dose may cause additive or synergistic effect, this were manifested the results of some neurobehavioral test in combined dosing groups that agreement with the study explain that the motor activity includes a broad class of behaviors reflecting the net integrated output of the sensory, motor, and associative processes of the nervous system **(18).** Motor activity is usually quantified as the frequency of movements over time. Effects of chemicals on motor activity are usually expressed as total number of counts or as a percentage of some control value (i.e., control group or pre-exposure baseline). The frequency of motor activity within a test session usually decreases, a phenomenon known as habituation. One major conclusion from motor activity is

ISSN NO: 2771-8840
Date of Publication: 04-09-2022

that the acute effect of most drugs is a depression of motor activity and that the hyperactivity may be evidence of a specific effect on the nervous system **(19).**

The fluctuated changes seen in the neurobehavioral study in this research might be due to under many system effect, this agreement with experiences that recorded that using a drugs as combination reflect the functional roles of the particular neurotransmitter(s) disrupts. Neuron affected by one or more neurotransmitters: dopamine, glutamate, serotonin, acetylcholine, and/or any of dozens of others that scientists have identified. Each neurotransmitter is associated with particular effects depending on its distribution among the brain's various functional areas. Neurobehavioral changes may also influence the Ach activity in the brain. Ach in the brain alter neuronal exitability, influence synaptic transmission, induced synaptic plasticity and coordination the firing of group of neuron. These action may explain the synaptic properties of neuron in several brain areas and discuss the consequence of this signaling on behavior related to drug abuse **(20).**

AchE activity that recorded inhibition in the most tested groups at 90 days of the experiment might be due to the effect of both drugs verapamil and colchicine that causes changes in the effect on the function of Ach neurotransmitters. Colchicine inhibits the synthesis and insertion of intracellular pools of AChRs into the sarcolemma **(12).** If a small number of newly synthesized AChRs or receptor-associated proteins are needed for receptor clustering to occur, then colchicine could block cluster reformation by preventing their incorporation into the sarcolemma. Verapamil was the most efficacious Ca2+ channel blocker tested in inhibiting ACh release, its effects being inversely correlated to the external Ca2+ concentration, Therefore, interference with cholinergic neurotransmission is likely to play a major role in the antipropulsive effect of verapamil, Under certain conditions sensitivity of cholinergic as well as adrenergic and glutamatergic neurons to Ca2+ channel blockers of different classes has been reported **(13**). The observation that calcium channel blockers cause concentration-dependent inhibition of muscle twitch, This finding suggests that verapamil, like curare, may have an effect on acetylcholine-activated ionic channels in the end-plate. **(14).** The primary site of action of verapamil is post-junctional. Clinical reports suggest that verapamil potentiates the neuromuscular blocking effects of neuromuscular blocking agents also found that calcium channel blockers potentiated a neuromuscular block, this explain the changes observed in neurobehavioral tests that resulted inhibition in many cognitive and locomotor activity. In order to interpret the mechanism of Ca2 + channel blocker motor inhibitory effects, it seem that verapamil supposed to act by opening or blocking Ca2+ channels were able to affect in opposite directions release of ACh from enteric neurons in a concentration dependent manner. In fact, verapamil is well known to bind toseveral neurotransmitter receptors, such as a1- and a2-adrenoceptors, muscarinic, and opioid receptors, and to block Na+ channels besides Ca2+ channels .All these properties could be responsible for the effects of verapamil on cholinergic neurotransmission **(15).**

The low level of Creatinine kinase that showed in colchicine alone and in combined by diminished efflux of enzyme into serum and cause weakness and reduce muscle mass . CK in serum may be inappropriately low because of reversible inactivation of enzyme thiol groups. This may be a consequence of release of the enzyme in a partly inactivated form or from CK inactivation within the circulation. Similarly, it was found that therapy with the antihypertensive drug captopril has been observed to produce low serum CK activity, possibly because of inhibition from disulfide metabolite formation **(16).** Golgi tendon organs (GTOs) monitor the tension produced by contraction to prevent excess forces by continuous feedback to the central nervous system (CNS). Thus, the CNS is informed by collective feedback mechanisms that include chemical, mechanical, and cognitive cues. The significance of each of these cues will depend on duration and power requirements of muscular activity. Depletion of ATP results in the leakage of extracellular calcium ions into intracellular space, due to both Na-K-ATPase and Ca2+-ATPase pump dysfunction. Intracellular proteolytic enzyme activity can increase and promote muscle protein degradation and augmented cell permeability, which allows some cell contents to leak into the circulation **(17).**

Conclusion: These results were attributed to the changes in the level of both drugs in brain and plasma and tissue due to their competitive inhibition of p-glycoprotein binding site in brain, plasma and tissue. Additionally. a significant effect of AchE activity that influences the Ach concentration both centrally and peripherally which might affect the cognitive, memory and motor activity of experimental animals.

ISSN NO: 2771-8840
Date of Publication: 04-09-2022

Acknowledgment:
Authors would like to thank the Ministry of Science and Technology \Baghdad for using their facilities to conduct this study. We also appreciate the technical assistance of their staff.

Conflict of Interest : The authors declare that there are no conflicts of interest regarding the publication of this manuscript

References:

1. Juliano , RL.; Ling, V. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. *Biochemistry Biophysiology* (1976). 455: p. 152-162.
2. Lin, J.H. Drug-drug interaction mediated by inhibition and induction of P-glycoprotein. Advance Drug Delivery. (2003). 55, p.53-81.
3. Moser,V.C.; Anthony,D.C.; Sette,W.F.; Macphial, R.C. Comparision of Sub-chronic Neurotoxicity of 2-hydroxymethyl acrylate and acrylamide in rat .Fundamental and Applied Toxicology , (1992).18:p.343-352.
4. Mohammed, F.K. and Omer, V.G. (1986). Behavioral and development effect in rat following utero exposure to 2, 4-d 12,4.5 mixture .Neurobehavioral. Toxicology and Teratology. 8: p.551-580
5. Mohammed ,F.K. (1984). Assessment of behavioral ,Neurochemical and development effect in developing rats following uterus exposure to non-mutagenic level of 2,4-d 12,4.5-t . Ph.D .thesis university of Missouri-Colombia, MO,USA.
6. Al-Backhoe, B. (2002). Neurobehavioral and biological changes induced by interaction of calcium and some insecticide in mice. PhD thesis, collage of veterinary medicine, Mosul university .Mosul , Iraq
7. Vohress, C.; Brunner, R.L.; Butcher, B.F. Psychotopic drugs as behavioral .Teratogenes. Science (1979). 205:p.12220-25.
8. Whishaw, I.Q. and Tomie, J.-A. Of mice and mazes: Similarities between mice and rats on dry land but not water mazes. Physiology. Behavioral. (1997). 60, p.1191–1197.
9. Deacon, R.M.J. Appetitive position discrimination in the T-maze. National Protocols (2006). 1, p.13–15.
10. Mueller KW. Possible captopril inhibition of creatinine kinase: a case report [Abstract]. Clinical Chemistry; (1985).p.31:941.
11. Devreotes, P. N., and D. M. Fambrough .Acetylcholine receptor turnover in membranes of developing muscle fibers Journal. Cell Biology. (1975). 65: 335-358.
12. Nordstrom, O., Braesch-and Ersen, S. and Bartfai, T. Dopamine release is enhanced while acetylcholine release is inhibited by nimodipine (Bay e 9736). Physiology. (1986). 126, p.115-119.
13. Bikhazgi, B. Florecs, Foldef, F.The effect of verapamil and EGTA on the rat phrenic nerve hemidiaphragm preparation. Anesrhesia and Analgesia .(1985) 64: p:8-505.
14. Changeux, JP. Allosteric receptors: from electric organ to cognition. Ann Rev Pharmacology and Toxicology; (2010).50: p.1–38.
15. Reiter, L.W., and Mac-Phail, R.C. Factors influencing motor activity easurements in neurotoxicology. In: Mitchell, C.L., ed. Nervous System Toxicology. New York: Raven Press, (1982). pp. 45-65.
16. Crofton, K.M.; Howard, J.L.; Moser, V.C.; Gill, M.W.; Reiter, L.W.; Tilson, H.A.; et al. Interlaboratory comparison of motor activity experiments: Implications for Neurotoxicological assessments. Neurotoxicology Teratology (1991). 13:599-609.
17. Khan, F.Y. Rhabdomyolysis: A review of the literature, ”Netherlands Journal of Medicine, (2009). vol. 67, no. 9, pp. 272–283.
18. Janis, R.A. and Scriabine, A. Sites of action of Ca+21 Channel inhibitors. Biochemistry. Pharmacology. (1983). 32, p. 3499-3507.
19. Ronis, MJJ.; Ingelman-Sundberg, M. Induction of human drug metabolizing enzymes: mechanism and implications. In: Woolf TF, editor. Handbook of Drug Metabolism. New York (NY): Marcel Dekker Inc, (1999). p. 62-239.
20. Meshorer, E.; Soreq, H. Virtues and woes of AChE alternative splicing in stress-related neuropathologies". Neuroscience. (2006)."29 (4): p.24-216.