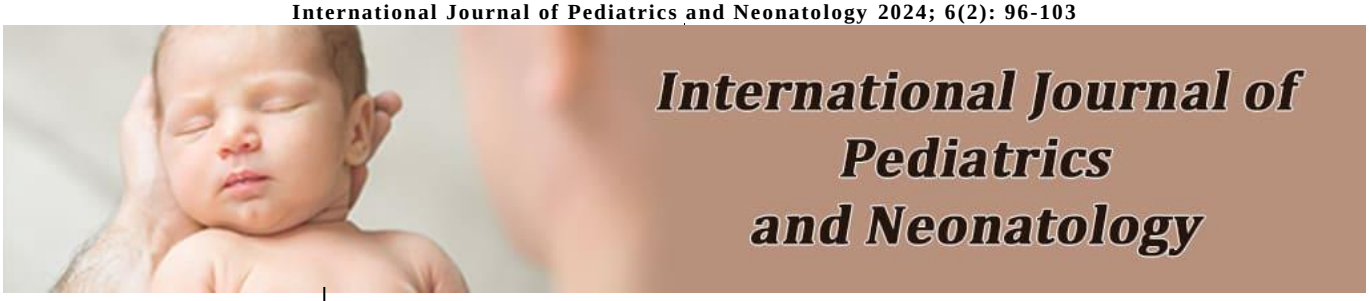

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The effect of koumine on social interaction and locomotion of a traumatic injury induced *Drosophila melanogaster* offspring model (Mimicking preterm birth defects)

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Abstract
Each year, around 15 million infants are born premature, often resulting in birth defects that affect social interaction and motor skills. The fruit fly, *Drosophila melanogaster*, serves as a model organism as its behaviors mirror premature birth defects, including anxiety, agoraphobia, and impaired movement. Maternal flies subjected to traumatic injury through a High Impact Trauma (HIT) device produce progeny with decreased social interaction and locomotion. Maternal trauma serves as a model for premature birth defects among fly progeny. Social interaction is assessed through a social space assay, which defines a fly's nearest neighbor as its social space. Shorter distances between flies indicate greater social interaction, as they tend to cluster more closely together. Locomotion is measured using a climbing assay, where the progeny flies are tested on their ability to perform negative geotaxis successfully. *Gelsemium sempervirens* (GS) extract administration improves social interaction levels among fly progeny mimicking preterm birth defects, and increased locomotion levels in the mice model for chronic stress. Koumine is a major chemical compound of *Gelsemium sempervirens* and the study investigates the chemical as the active ingredient driving the increase in social interaction and locomotion. My hypothesis that administering koumine to maternal flies with traumatic injury improves social interaction and locomotion levels in progeny is supported by the significant differences observed. Fly progeny exhibited increased social interaction and locomotion when koumine was administered at the maternal level. The research provides a pathway for novel drug discovery, employing koumine as a treatment for premature birth defects in neonates.

Keywords: Premature birth, birth defects, social interaction, motor skills

1. Introduction

1.1 Premature Birth

Around 15 million infants are born premature each year (WHO, 2022) [17]. Premature neonates may face a range of birth defects that can affect their overall health and quality of life, including diminished social interaction, heightened anxiety, and delayed motor development (Crnic *et al*., 1983) [3]. Infants born premature have exhibited significant signs of neurodevelopmental impairment through cognitive delay and poor locomotive behavior during early-life stages (You *et al*., 2019) [19]. The presence of locomotive delay among premature babies often results in a decrease in specific motor skills such as accurate posture and crawling (Ko & Lim, 2023) [13]. Neonates may go through speech therapy and physical therapy to alleviate symptoms of reduced social interaction (Including impaired speech) and decreased locomotive ability (Johnson, 2007) [11]. Reduced social interaction in neonates is frequently linked to diminished parent-infant interaction (McCollum, 1984) [14]. Very preterm (VPT) children show lower cognitive abilities during adolescence compared to children carried to full-term (Johnson, 2007) [11]. The decline in cognitive skills is often accompanied by impaired socioemotional development. VPT children with reduced socioemotional development may experience decreased social competency and less interactive behavior, as evidenced by research on early-life children (Groh *et al*., 2017) [9]. Impaired locomotion has a clear association with decreased social interaction among VPT infants and can lead to a higher risk in socio-developmental issues in early-life stages (You *et al*., 2019) [19].

1.2 Maternal Trauma

Traumatic injury (TI) during pregnancy is a significant risk factor associated with developmental disabilities in children. Around 50% of maternal injuries arise from incidents like motor vehicle accidents (Esposito *et al*., 1989) [6]. Studies involving pregnant women reveal that those who suffer physical traumatic injury are more likely to experience early preterm birth due to fetomaternal hemorrhage (Drost *et al*., 1990) [5]. This type of injury can lead to delays in socioemotional and motor development in prematurely born infants (Goodwin & Breen, 1990) [8]. Currently, no pharmaceutical treatment exists to address developmental defects in neonates resulting from maternal trauma.

1.3 Model Organism

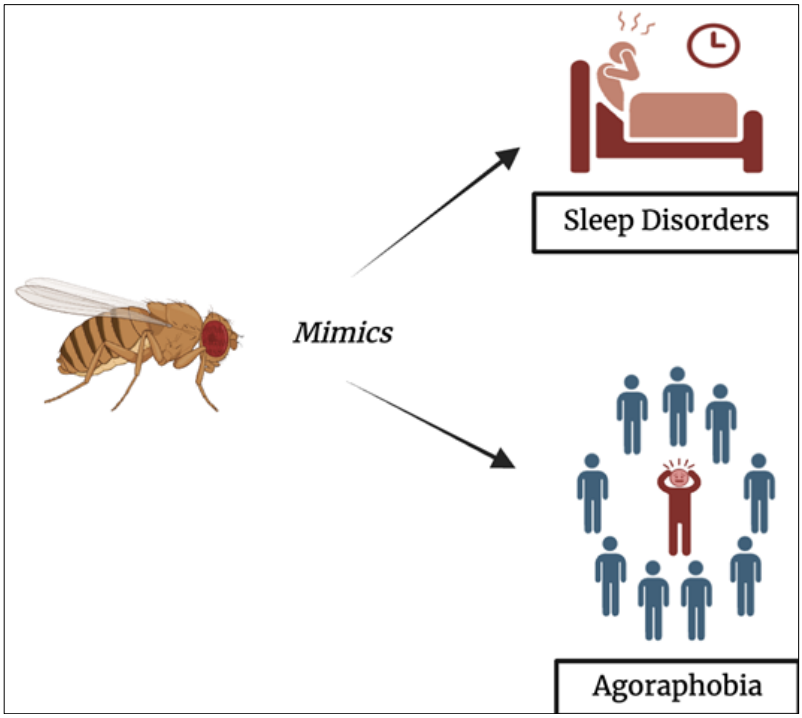

Fig 1: *Drosophila melanogaster* mimics premature birth defects (Das, 2024) [4]

The fruit fly, *Drosophila melanogaster*, serves as an effective model organism for investigating developmental behavior due to its ability to replicate various social behaviors found in humans. Researchers use *D. melanogaster* to study human behaviors linked to preterm birth, including depression, anxiety, agoraphobia, reduced sleep quality, neophobia, and impaired motor skills (Meichtry *et al*., 2020) [15]. By examining these behaviors in fruit flies, we can better understand how birth complications influence social interactions and lead to behavioral changes (Chauhan & Chauhan, 2019) [2].

1.4 Measuring Social Interaction & Locomotion

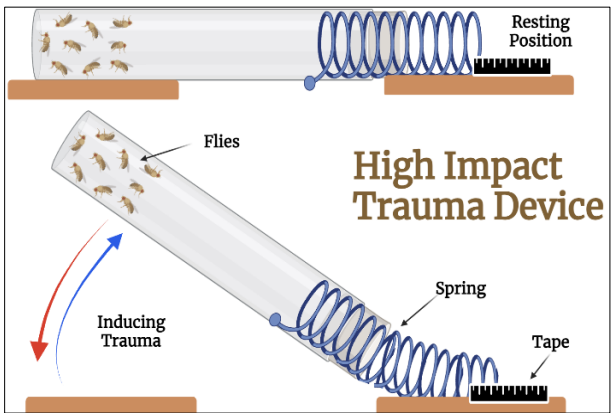

Fig 2: High Impact Trauma device for maternal trauma (Das, 2024) [4]

Researchers have studied the effects of traumatic injury (TI) in fruit flies and how it influences the social behavior of their offspring. TI can be triggered in flies using a High Impact Trauma (HIT) device, which employs a closed head traumatic brain injury technique (Katzenberger *et al*., 2013) [12], as illustrated in Figure 2. A study investigating maternal TI in fruit flies revealed a reduction in social interaction and locomotion among the progeny (Chauhan & Chauhan, 2019) [2].

A social space assay quantifies individual levels of social interaction by measuring the distance between each fly and its nearest neighbor, referred to as the social space distance (Simon *et al*., 2012) [16]. Greater social space distances among fly offspring indicate social isolation, reflecting behaviors associated with increased anxiety and timidness, while smaller distances and closer aggregation signify higher levels of social interaction (Chauhan & Chauhan, 2019) [2]. To measure these social space distances, a triangular-shaped test chamber is employed, as it offers the most reliable model for evaluating social interaction based on the relative clustering of flies (Simon *et al*., 2012) [16]. Through recording social space distances of fly progeny, social interaction levels can be used to be appropriately assessed as the distances provide an indication to the aggregation of flies.

A climbing assay is used to test locomotion in TI progeny by measuring their ability to perform negative geotaxis. Fly progeny with decreased motor ability have a strong correlation with a decreased social competency (Chauhan & Chauhan, 2019) [2]. Through recording pass rates of fly

progeny, locomotion levels can be appropriately assessed as it provides an indication to the motor ability of flies based on performing negative geotaxis.

1.5 Koumine Treatment

Gelsemium sempervirens (GS) extract is a recognized herbal remedy used in adult humans to relieve anxiety at ultralow doses (Yu *et al*., 2022) [20]. In the mice model for chronic stress and anxiety-like behavior, GS administration led to an improvement in locomotion and decrease in neophobia suggesting a correlation with adaptation to novel social environments (Bellavite *et al*., 2011) [1]. Administering *Gelsemium sempervirens* (GS) to TI-induced maternal fruit flies significantly enhanced social interaction levels in their offspring, which mirrored preterm birth defects.

Koumine (KM) is one of the major chemical compounds of the alkaloid class present in GS and is known to possess similar anti-anxiety abilities as GS (Yu *et al*., 2022) [20]. Koumine has alleviated anxiety-like behavior and decreased neuropathic pain without inducing adverse neurological effects in the sound-stress induced rat model (Xiong *et al*., 2022; Jin *et al*., 2018) [18, 10]. Investigation into koumine allows for the potential of therapeutic options using the chemical compound with more targeted effects as opposed to administrating the herbal GS extract at ultralow doses (Yu *et al*., 2022) [20]. Therefore, it is hypothesized that an administration of KM to maternal fruit flies with TI, will result in progeny with improved social interaction and locomotion levels.

1.6 Novelty & Purpose

The purpose of the study is to investigate koumine as a potential treatment and active ingredient of *Gelsemium sempervirens* to improve social interaction and locomotion of a maternal TI induced *Drosophila melanogaster* offspring model. Since koumine has not been utilized in flies as a therapeutic nor has it been explored at alleviating preterm birth defects (In a neonatal model) it is a novel study. In addition, koumine has not been previously determined as the active ingredient that drives the increase in social interaction and locomotion among fly progeny. Investigation into koumine as the potential active ingredient of GS, creates a possible precursor to drug discovery as it supports drug development with more targeted effects in treatment.

Ultimately, the research creates a pathway for further research on newborns who experience premature birth defects with a means for therapy through koumine. Neonates can potentially benefit from koumine as the pregnant women do not have to rely on ultra-low doses of the extract and instead use the major chemical compound to produce more targeted improvements in the progeny.

2. Methods

2.1 Stock Maintenance

Wild Type Oregon-R flies, sourced from Carolina Biological Supply Company, were maintained at 22 °C on a standard cornmeal and agar diet, with a 12-hour light/dark cycle. The fruit flies were transferred into fresh plastic vials with foam plugs every four days. Every three weeks, the flies were moved into vials containing a fresh batch of fly food. For disposal, the flies were refrigerated for about an hour before being discarded in the trash.

2.2 Fly Food Preparation: Dry ingredients were measured using an electronic balance, scoopula, and weigh boat: 6.75 grams of yeast, 3.90 grams of soy flour, 28.50 grams of yellow cornmeal, and 2.25 grams of agar. Wet ingredients, including 30 mL of light corn syrup and 390 mL of distilled water, were measured with a graduated cylinder. The dry and wet components were combined in a 500 mL beaker and mixed thoroughly with a stirring rod. The mixture was then heated in a microwave in 30-second intervals until it reached a rolling boil, with frequent stirring using a glass rod between each interval. Once boiling, the mixture was allowed to cool to approximately 15 °C to 20 °C, as verified with a thermometer. After cooling, 1.88 mL of 10% propionic acid was added with a micropipette. The resulting food was distributed into approximately 30-40 vials and covered with cheesecloth to avoid contamination while cooling to room temperature. The vials were checked daily for mold or other contaminants, and any affected vials were discarded. For the treatment food, 150 microliters of koumine was added to the maternal fruit flies alongside the 10% propionic acid.

2.3 Cold Sorting

To cold sort the flies, the contents of each vial were transferred into a new vial and placed in an ice bucket for about 2 minutes. The flies were then separated by gender using a feather on the *Teca* cold sorting machine set to 2 °C. To ease their transfer to the social space assay apparatus, female flies were cold anesthetized and kept isolated.

2.4 Koumine Administration

Koumine, sourced from SelleckChem, was added to the fly food for female fruit flies. The koumine was diluted for flies according to the mass-to-dosage ratio used for humans. After scaling up hundred-fold from an initial concentration of 1.5 microliters per batch, 150 microliters were administered to a set of 100 food vials using a micropipette.

2.5 High Impact Trauma Device

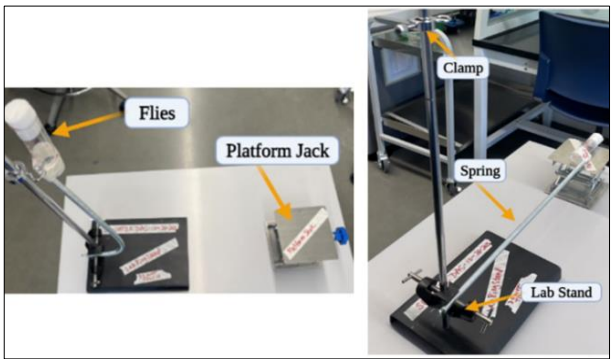

Fig 3: Maternal trauma device constructed (Das, 2024) [4]

The High Impact Trauma (HIT) device was designed to induce traumatic injury (TI) in female fruit flies and serves as a model for traumatic brain injury. The construction of the HIT device follows the setup detailed in the experimental diagram (Figure 3). This procedure is adapted from methods described by Katzenberger *et al*. (2013) [12] and Chauhan & Chauhan (2019) [2] and includes a 32 cm screen door spring, a platform jack, a lab ring stand, and clamps. Before each trial, maternal flies were transferred into an empty vial. During each trial, the vial containing 15-20 flies was released five times in succession against the platform jack to apply a consistent force across trials.

2.6 Social Space Assay

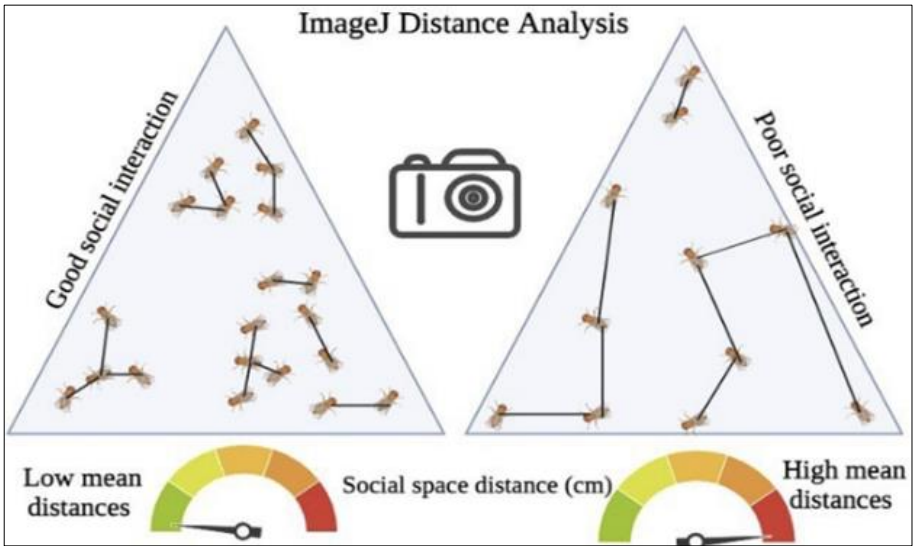

Fig 4: Social space assay methodology (Das, 2024) [4]

Female offspring, aged 4-5 days, were sorted and placed into a triangular test chamber (14.87 cm x 12.7 cm x 1.27 cm) after cold sorting. Females were chosen due to their more reliable interaction and movement patterns compared to males. The flies were left in the chamber for 20 minutes to ensure sufficient social interaction and a consistent social space distance. Following this period, an image of the fly aggregation was taken (refer to Figure 4). Each social space assay included around 15-20 flies. The image was then analyzed with ImageJ software, using a scale set to the chamber's height of 14.87 cm. The average social space distance for the female offspring was recorded as one trial. A lower average distance signified higher social interaction, with flies more closely packed, while a higher average distance indicated lower social interaction, with flies more spread out.

2.7 Climbing Assay

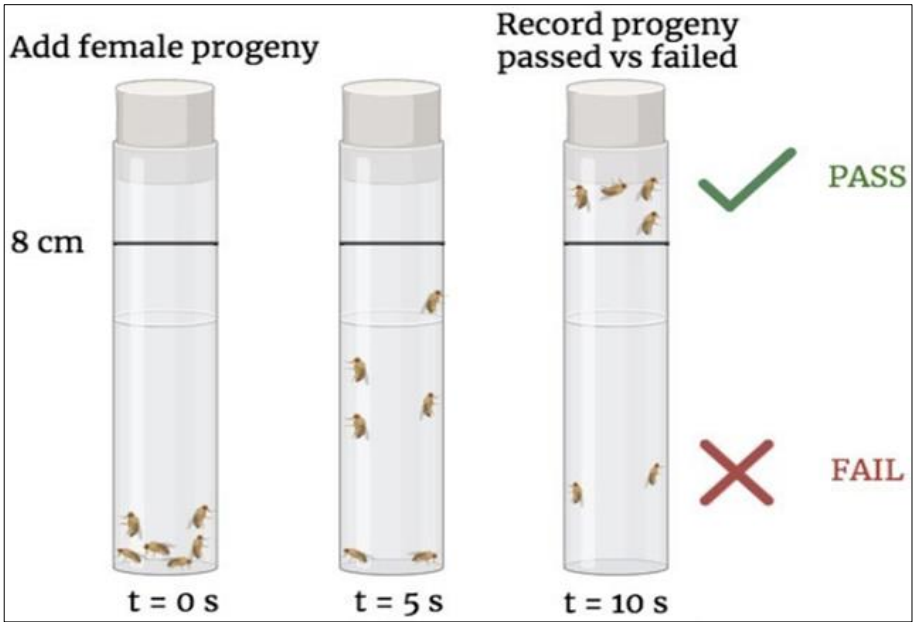

Fig 5: Climbing assay methodology (Das, 2024) [4]

4-5 days old female progeny were sorted and transferred into empty vials and closed with flug. The progeny flies were allowed to acclimate for one to two minutes under the novel conditions and a mark was drawn at 8 cm from the top of the vial using a marker. After tapping the vial firmly against the surface so all flies are at the bottom, the vial was flipped upside down and a ten-second timer was started simultaneously. Each vial typically contained around a sample size of 10 flies. Using a video camera to record how many flies passed the 8 cm mark over the 10 seconds, a pass rate was calculated for the female fly progeny (Refer to Figure 5). If a fly passed the 8 cm mark and fell back down, it was counted as a pass. A higher pass rate for progeny flies, suggested better locomotion levels as opposed to lower pass rates.

3. Results

3.1 Groups & Expected Results

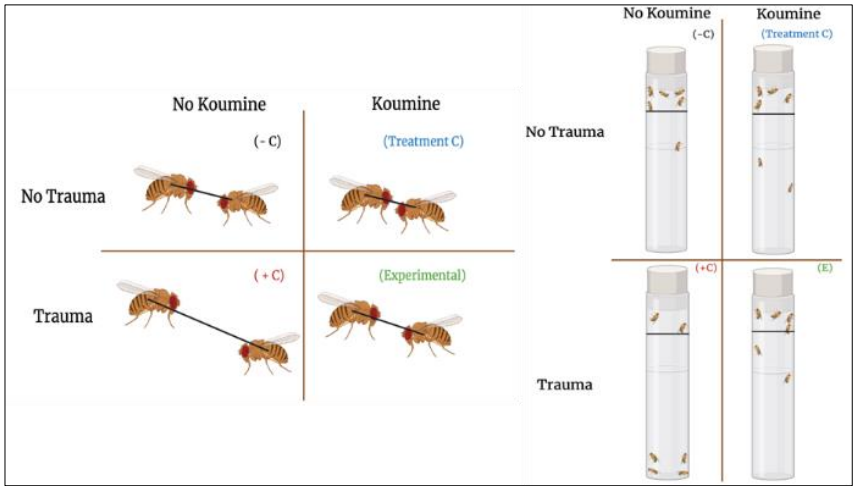

Fig 6: Shown on the left is groups and expected results for social interaction and displayed on the right is for locomotion (Das, 2024) [4]

The positive control is when no koumine is administered with the presence of maternal trauma. The negative control group is where there is no koumine treatment and no maternal trauma administered. The purpose of the negative and positive control group is to test if HIT device is effective and the maternal trauma model works, when testing the defects of fly progeny. The expected outcomes of the negative control group involve establishing a normal social interaction and locomotion level of fly progeny. The expected outcomes of the positive control group include a decreased social interaction level and lower climbing assay pass rate due to the presence of TI (refer to Figure 6). The treatment control group is when there is koumine present but no maternal trauma administered. The purpose of the treatment control group is to test if the koumine compound is toxic to the fly progeny. The experimental group is when there is both koumine and maternal trauma present. The purpose of the experimental group is to see if the treatment significantly improves social interaction and locomotion of fly progeny compared to when there is no treatment under the maternal trauma model (Positive control).

3.2 Data

Each group, as illustrated in Figure 6, underwent ten trials of both social space assays and climbing assays. The mean progeny social space distances, measured using ImageJ, were recorded and are displayed in Table 1. The progeny pass rates calculated for each trial are shown in Table 2. An asterisk (*) in Figure 7 and Figure 8 resembles a significant difference ($p < 0.05$ for a two-tailed test) in either social interaction or locomotion.

Table 1: Mean social space distances (cm)

Trial	No Trauma & No Koumine	No Trauma & Koumine	Trauma & No Koumine	Trauma & Kournine
1	1.5639	0.9263	1.9975	0.7655
2	1.0127	1.6732	2.1227	1.1992
3	1.2078	1.1021	4.2679	0.6772
4	1.0896	0.8754	2.2017	1.6742
5	1.4995	1.0134	1.7674	1.1942
6	1.2335	1.0476	1.8951	1.5281
7	1.2812	0.9724	3.6789	1.8456
8	1.2774	1.7821	1.8997	1.7951
9	1.0702	1.4432	2.2054	0.9457
10	1.0245	0.9516	1.7705	1.2425
Group Averages:	1.226	0.9263	1.9975	0.7655

Table 2: Average locomotion performance (%)

Trial	No Trauma & No Koumine	No Trauma & Koumine	Trauma & No Koumina	Trauma & Koumine
1	60	60	10	50
2	70	80	18.2	50
3	81.23	50	30	60
4	70	66.67	25	45.45
5	60	66.67	16.7	46.15
6	80	71.12	9.09	50
7	80.11	75	10	70
8	70	66.67	20	55.56
9	71.23	82.13	16.7	50
10	66.67	60	27.3	50
Average pass rates	70.924	67.826	18.29	52.72

3.3 Graph of Average Social Space Distance Comparison

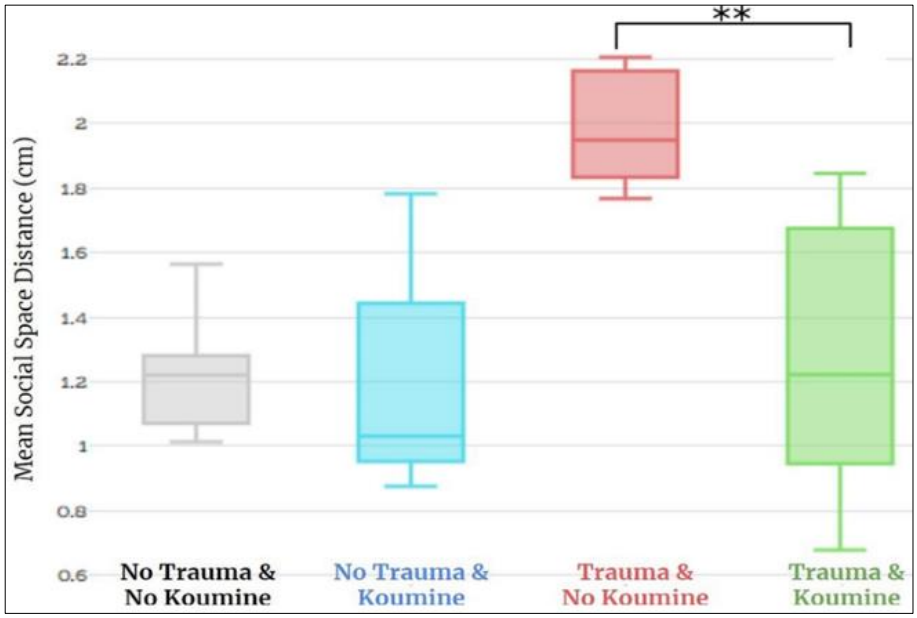

Fig 7: Koumine significantly improves progeny social interaction.

3.4 Graph of Locomotion Pass Rate Comparison

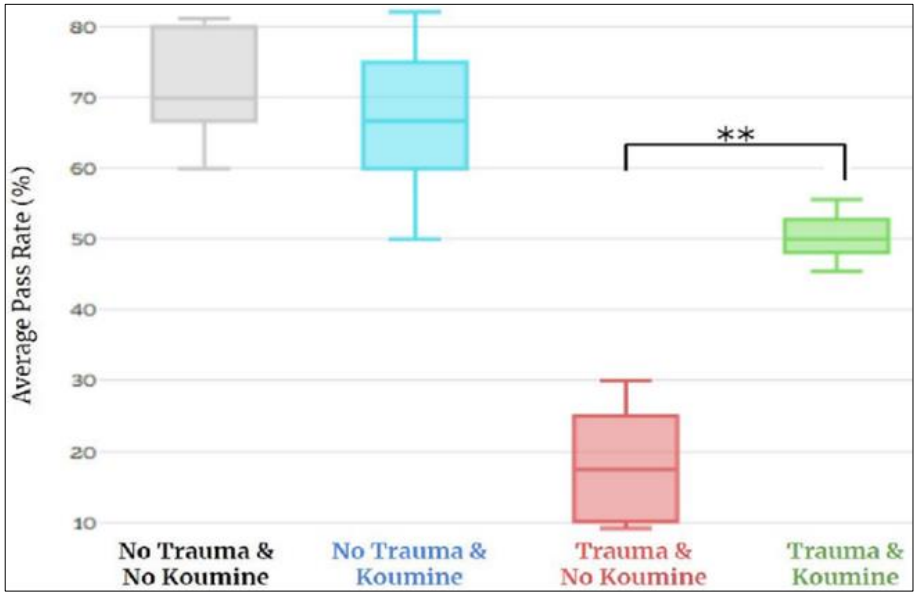

Fig 8: Koumine significantly improves progeny locomotion.

3.5 Statistical Analysis

Figure 7 displays the distribution of average social space distances over ten trials for each data collection group, as detailed in Table 1. Figure 8 shows the distribution of progeny pass rates across ten trials for each data collection group, corresponding to the information in Table 2. Table 3 provides the p-values obtained from the Mann-Whitney U Test used for statistical analysis. An asterisk (*) next to a p-value indicates a significant difference ($p < 0.05$ for a two-tailed test) in either social interaction or locomotion.

Table 3: Mann-Whitney U Test P-values

Comparison	Social infraction	Locomotion
No Trauma & No Koumine VS. No trauma & Koumine	0.2713	0.4715
Trauma & No Koumine VS. No Trauma & No Koumine	0.00018*	0.0002*
Trauma & No Koumine VS. Trauma & Koumine	0.00058*	0.00018*
No Trauma & No Koumine VS. Trauma & Koumine	0.8493	0.0009*

4. Discussion

4.1 Data Analysis: The p-value of 0.2713 and 0.4715 between "No Trauma & No Koumine vs. No Trauma & Koumine" suggests that there is no significant difference in social interaction and locomotion when koumine is used in the absence of trauma, which shows that the treatment is not

toxic. P-value of 0.00018 and 0.0002 between "Trauma & No Koumine vs. No Trauma & No Koumine" suggests a significant difference in social interaction and locomotion, validating the maternal trauma model. A p-value of 0.00058 and 0.00018 between "Trauma & No Koumine vs. Trauma & Koumine" indicates there is a significant difference in social interaction and locomotion, which means koumine improves interaction and locomotion. The p-value of 0.0009 shows that there is no significant difference in social interaction, which indicates that koumine in a trauma model results in interaction levels close to normal.

4.2 Connection to Current Research

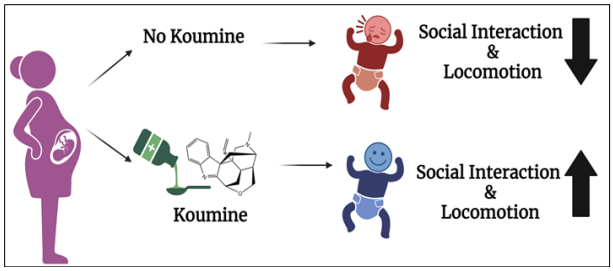

Fig 9: Future potential outcomes for koumine administration in prenatal period versus no koumine utilization (Das, 2024) [4].

Since koumine was identified as a treatment for increasing social interaction and locomotion in progeny flies mimicking preterm birth defects, the research creates a pathway for future research on neonatal interaction and motor ability. By identifying koumine as the active ingredient responsible for driving the improvements in interaction and locomotion a novel treatment has been discovered. Koumine presents a therapeutic option to alleviate preterm birth defects and improve psychological development in neonates. Koumine could act as a precursor to drug discovery as the findings elucidate the possibility of future studies on pregnant women utilizing koumine during the prenatal period (Refer to Figure 9) to alleviate possible decreased social interaction and locomotion in neonates.

4.3 Limitations & Errors

The koumine treatment dosage could be a potential limitation as it was based on mass ratio calculation as there were no previous studies incorporating koumine with flies. The limitation of dosage of koumine made it difficult to establish a baseline for the appropriate toxicity level for flies. The delivery of trauma induced by the HIT device was initially limited due to challenges in controlling the force applied to the flies consistently. To mitigate the issue and maintain an approximately constant spring force, a platform jack and clamps were utilized.

4.4 Future Work: Potential future areas of research include studying alternative mimicked premature birth defects in *D. melanogaster* such as decreased sleep quality and duration in relation to sleep disorders (ie. sleep apnea) in neonates. Another avenue for future work involves furthering the drug development of koumine by researching in the clinical sector to progress the potential for koumine as a prenatal supplement.

5. Conclusion

Maternal fruit flies that underwent traumatic injury (TI) and received koumine treatment produced offspring with enhanced social interaction and locomotion, in contrast to offspring from untreated, TI-exposed maternal flies. Therefore, the scope of the project is met and the hypothesis is supported as koumine was identified as a valid treatment and active ingredient for improving both social interaction and locomotion for progeny flies mimicking preterm birth defects. The research provides a pathway for novel drug discovery by employing koumine as a potential treatment for premature birth defects in neonates.

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7. Conflict of Interest: Not available.

8. Financial Support: Not available.

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