How Modifications in Ethnic Diet Can Alter Drug Efficiency in Individuals

Grant Proposal

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Abstract (RQ)

Imagine if doctors could give you your perfect treatment on the first try. Often, when doctors prescribe medicine, the trajectory of healing is not linear. Each drug has a unique effect on each patient, which is largely determined by genetic mutations unique to each individual. This relationship between genes and drug response is examined in pharmacogenetics. Specifically, mutations in the cytochrome P540 (CYP) family of genes, notably CYP3A4 and CYP3A5, are crucial because they influence an individual's metabolic rate. However, the expression levels of these genes can be manipulated by various external factors, such as diet, which is studied in nutrigenetics. While individual, regulated genetics could help tailor treatment plans and reduce adverse drug reactions, implementing pharmacogenetics raises several concerns. These include issues like cost, the need for standardized guidelines, and provider education, all of which require further research. Currently, most pharmacogenetic data are limited to males of European descent, which inadequately represents the global population. This limitation ignores geographic-specific patterns, suggesting that certain populations or regions exhibit identical characteristic traits in metabolism speed and drug response. To investigate how ethnic dietary compounds, such as curcumin and ellagic acid, affect CYP gene expression and drug response, Drosophila melanogaster was used as a model organism. The reasons are their ease of manipulation, low cost, fast reproduction rate, and, most importantly, their 75% homology to human disease genes. First, the behavioral impact of the diets was assessed through their total food intake of a sucrose and ethanol solution, which was correlated to locomotion using climbing activity and wing usage assays. Ethanol operated as a mock drug, visibly slowing down the flies. This data implied active changes in metabolism, later confirmed with an RT-PCR test. By combining the determined changes in gene expression and the behavioral impact of diet on drug response, both effects can be weighed to develop realistic treatment strategies. Throughout this process, curcumin showed significant changes in food intake, energy, and climbing, with increases of a 78.59%, 15,036%, 83.99% from the control, respectively ($p \approx 0.037$, $p \approx 0.0053$, $p \approx 0.015$). Likewise, ellagic acid resulted in baseline increases of 12.25%, 5,102%, and 142.11% ($p \approx 0.031$, $p \approx 0.0087$, $p \approx 0.03$). Collectively, this data could provide insights into meaningful interactions between diet, genes, and drugs, and serve as a step toward creating culturally informed medical decisions.

Keywords: Pharmacogenetics, Drosophila Melanogaster, Cytochrome P450 alleles, Drug, Genes, Specialized Medicine

How Modifications in Ethnic Diet Can Alter Drug Efficiency in Individuals

While one medical treatment plan may easily resolve the issues of one patient, the same treatment may be ineffective or introduce complications in another. This reality of varying therapeutic effectiveness, reflected in patients, is made true through pharmacogenetics, which is the idea that a person's genetic information can influence the way their body processes drugs. Every person has their own DNA, passed down from parent to offspring, which is like their own unique fingerprint. This unique identity is constructed through variations in DNA. Variations such as these often consist of SNPs, or single-nucleotide polymorphisms, which are defined as variations of single nucleotides in a genome, or CNVs, which are differences in the number of copies of specific DNA segments, encompassing deletions, insertions, or duplications of DNA (He et al., 2011). Both alter enzyme activity, thus helping to determine an individual's unique reaction to specific medications.

Cytochrome P450 Alleles:

Building upon this concept, scientists have made note of genetic variants, such as those in the cytochrome P450 (CYP) family, that play critical roles in the transport and detoxification of xenobiotics. Humans carry 57 functional CYP genes that fit into 18 major families, many critical ones belonging to the CYP2 and CYP3 families (Swen et al., 2023). They code for enzymes that are crucial in metabolizing medicine and are largely polymorphic, meaning they provide insight into adequate patient treatments. Variations in the CYP genes determine the rate at which an individual will digest and absorb medication, a part of the pharmacokinetic cycle consisting of absorption, dilution, metabolism, and excretion. Within this scope, there are four major classifications of metabolism: ultra-rapid, normal, intermediate, and poor (Zhou & Lauschke, 2022). This information can be used by medical professionals to limit adverse drug effects through appropriate adjustment of drug doses.

However, not all populations exhibit the same genetic variants of CYP enzymes. Although these alleles have a high frequency, geographic location has proven to be a factor in their distribution. This factor implies that people from the same population may exhibit patterns in their metabolic rate. Examples were found in a European study of 6,944 patients who underwent genetic testing prior to treatment. The scientists noted that CYP2D6 alleles were found in 44.6% of people, and numerous genes had differing frequencies in varying populations (Swen et al., 2023). From a global lens, another study involving 141,614 people from 12 distinct populations further confirmed

that a gene's minor allele frequency (MAF) is not constant (as seen in Figure 1), suggesting that while a MAF value might apply to a specific population or group of people, it may not apply to others (Zhou & Lauschke, 2022).

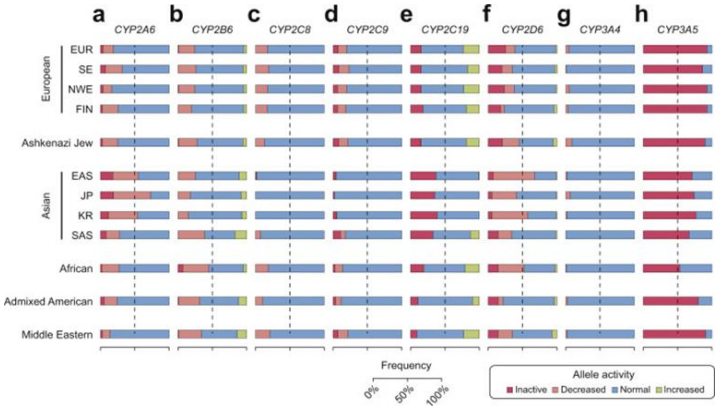

Figure 1. Frequencies of CYP alleles. This graph displays the frequency of inactive, reduced activity, normal, and increased activity alleles in 8 genes from the CYP2 and CYP3 families. Rows represent populations of European (EUR, SE, NWE, FIN), Ashkenazi Jewish, East Asian (EAS, JP, KR), South Asian (SAS), African, Admixed American, and Middle Eastern ancestry, which show additional inter-population variation (Zhou & Lauschke, 2022).

The variation in CYP allele frequency characterized here implies that metabolic differences are biologically rooted and may interact with factors, such as diet. This supports the idea that medical standards of care should be dependent on the patient's ethnic population and background (Zhou & Lauschke, 2022).

Diet:

Specifically, diet is a large defining factor of ethnic populations. While genetics plays a large role in gene expression, diet does also. Frequent consumption of foods native to geographic locations can create patterns in the altered expression of CYP genes (Martinez-Lomeli et al., 2023). Two examples of ingredients that shape gene expression are curcumin and ellagic acid. Curcumin, the bioactive ingredient in turmeric and a prevalent spice in South Asia, is known for its flavor and medicinal properties, such as being antioxidant and anti-inflammatory (Kocaadam & Şanlier, 2017). Similarly, ellagic acid is a bioactive ingredient found in high concentrations in pomegranates, a fruit commonly eaten in Middle Eastern countries, such as Turkey.

RNA Interference:

To understand how these dietary components might influence gene expression, genetic manipulation with the use of RNA interference (RNAi) is pivotal. RNAi is a precise tool that silences specific genes using small RNA molecules that destroy messenger RNA, stopping the creation of proteins. This tool can artificially model populations with inactive genes, more accurately measuring results specific to the location.

Drosophila Melanogaster as a Model:

To model this effectively, Drosophila melanogaster will be used. This species of fruit flies was chosen to represent humans due to their low cost, short lifespan, and ability to be genetically modified (Munnik et al., 2022). However, the most prominent rationale behind using Drosophila is that 178 of 286 human disease genes are conserved in Drosophila, meaning that fly responses can be correlated to human behaviors (Fortini et al., 2000).

Implementation of Pharmacogenetics:

Ultimately, this fly model has the potential to prove the importance of pharmacogenetics as well as kickstart its eventual implementation. Though pharmacogenetic application has already shown a reduction of adverse drug events (Fig. 2), several barriers remain (Swen et al., 2023). First, the cost efficiency has not been determined. A study of 5,288 savings of up to $7,000 in direct medical costs; however, this estimate does not cover the cost of time, gene tests, or insurance (Swen et al., 2023). Furthermore, there has been minimal clinical testing validating pharmacogenetic impact, a lack of standardized guidelines, and a lack of movement towards education of this resource. (Scott, 2011).

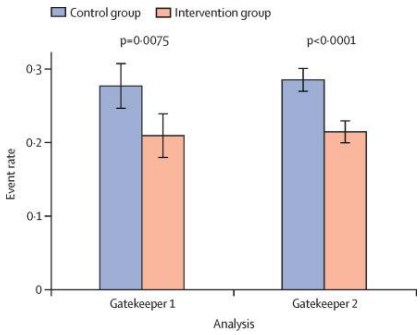

Figure 2. The difference in adverse drug reaction frequencies of 6944 individuals in a study who received pharmacogenetic testing and those who did not. In both trials, the risk of adverse drug reactions was reduced by 30%, signifying a noteworthy reason to employ pharmacogenetics in medical practice (Swen et al., 2023).

Addressing these gaps, this project looks at what could be a root cause of adverse drug effects. It explores why people react to drugs differently, bridging pharmacogenetics and nutrigenetics. Furthermore, it considers shared environmental factors in people, or even countries, providing next steps for pharmacogenetics that are reasonable considering preexisting knowledge and limiting factors.

Section II: Specific Aims

This project's objective is to determine how diet impacts an individual's response to drugs, with a long-term goal of applying findings to pre-existing CYP pharmacogenetic data to improve health outcomes. The central

hypothesis is that if the consumption of geographic compounds, such as curcumin and ellagic acid, affects xenobiotic sensitivity, then the medical course of action should be altered because humans are equipped with natural variations in their level of expression of CYP alleles, which are further altered by diet.

The rationale is that CYP genes are highly conserved and vital in pharmaceutical metabolism. Current pharmacogenetic studies are conducted through a genetic variation lens, raising ethical concerns. However, if dietary constituents alter metabolic enzyme activity, a new factor in specialized medicine will be introduced. The consideration of ethnicity and diet alongside DNA polymorphisms potentially improves drug effectiveness.

The work we propose here will use Drosophila as a model organism to investigate interactions that occur between geographic-specific diet, CYP genes, and drugs, providing insight as to how human dietary intake influences metabolic outcomes.

Specific Aim 1: Determine if dietary intake affects physical drug behavioral response by exposing the Drosophila to curcumin, ellagic acid, or sucrose for 6 days, supplying them with ethanol (as a mock pharmaceutical drug), and assessing their locomotion and food intake.

Specific Aim 2: Determine whether ellagic acid and cumin change CYP6a2, CYP6a8, or CYP6g1 gene expression through comparison of RT-PCR results of flies fed sucrose and flies fed curcumin and ellagic acid.

Specific Aim 3: Determine if changes in drug outcomes due to ethnic ingredients are heightened or reduced across populations. Physical behaviors will be assessed with RNAi flies to reflect natural variation.

The expected outcome is to identify both curcumin and ellagic acid as modifiers to specific CYP genes through RT-PCR tests and behavioral responses. Noted behavioral and genetic changes can be applied to human populations and further provide medical professionals with information on how to optimize drug performance.

Section III: Project Goals and Methodology

Relevance/Significance:

Despite the advances of modern medicine, one of the biggest challenges is accounting for variability in drug response. This challenge not only introduces higher long-term costs and health risks but is also detrimental to doctors. While it is understood that genotypes determine drug response, additional information can help medical professionals align drug prescriptions and dietary recommendations to maximize both overall health and treatment outcomes. Implementing genetic testing as a standard of care, however, would introduce numerous complications,

starting with a lack of information about next actionable steps, inadequate testing facilities, disruptions to pre-existing medical procedures, privacy concerns, economic barriers, and known overall efficacy. In the future, these findings that link nutrigenetics and pharmacogenetics can be used to fuel the eventual and gradual transition into specialized medicine and be used to determine more about weight loss, athletic performance, high blood pressure, cholesterol levels, and caffeine responses, among many other phenotypes (Shaman, 2024).

Innovation:

The project is innovative because it bridges pharmacogenetics with nutrigenomics (diet-gene interactions), which has not been thoroughly researched in connection with disease and specialized medicine. As of now, a majority of pharmacogenetic studies, such as Swen et al. (2023), are limited to the effect of genetic testing on drug response, which is reliant on European data, disregarding other unique populations (Gray, 2024). The effect of ethnic dietary compounds on gene expression, metabolism rate, and physical response to medicine could allow medical professionals to create culturally informed patient outcomes and treatments. Furthermore, these observations can be integrated with preexisting CYP MAF data to make inferences on ideal treatment dosages with increased accuracy.

Methodology:

To assess the effect of diet on behavioral drug response, Drosophila will be fed sucrose, curcumin, or ellagic acid media for six days. They will then be anesthetized by CO_2 and put into vials with four capillaries of 10μL of a 5% sucrose and 10% ethanol solution each, composing a capillary feeder assay. An empty vial with one capillary will be an evaporative control. After a day, 4 times the displacement of the evaporative loss is subtracted from the total displacement in each experimental vial, determining the total food. Climbing ability and energy levels will be averaged over 3 trials through the number of flies that can climb above 12cm in 10 seconds and the number of wing usages in each vial in 1 minute, respectively. This process will be repeated for each RNAi fly strain.

To determine gene expression changes, flies fed their assigned diet for at least 6 days will be tested with RT-PCR. Gene activity changes will be determined through comparison of the control group with each of the experimental groups containing curcumin and ellagic acid.

***Specific Aim #1*:** Determine if dietary intake affects behavioral drug response. The objective is to look at the wild-type Drosophila's response to ethanol in differing diet groups. Our approach is to feed the flies sucrose, curcumin, or ellagic acid for 6 days, then expose them to ethanol and compare their locomotion (climbing and energy levels) to those on the control diet. Our rationale for this approach is that diet may alter gene expression and metabolism, inducing physical changes and determining if bioactive ingredients and nutrition impact drug response.

Justification and Feasibility:

The goal of this aim is to compare three diets and their response to a drug, ethanol. A Wiley article displays diets with yeast alter ethanol sedation time (Figure 3), supporting this aim (Schmitt et al., 2020). Our rationale is that if bioactive ingredients have modulatory effects on metabolism and ethanol sensitivity, there will be notable physical behaviors in Drosophila.

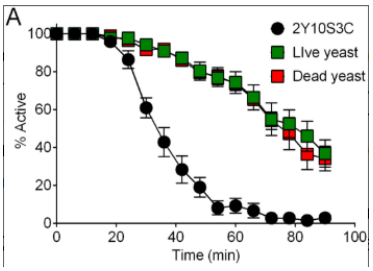

Figure 3: Percentage of active female Drosophila fed live or dead yeast paste over time after ethanol exposure. Activity duration is dependent on diet (Schmitt et al., 2020).

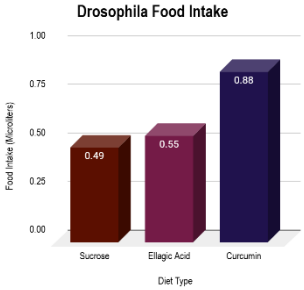

Figure 4: Ethanol and Sucrose Solution Intake Per Fly in a Capillary Feeder Assay. Flies that were preconditioned on the 0.5% curcumin diet had the highest intake, with a mean of 0.88 microliters, compared to 0.55 microliters of the 200μM ellagic acid group and 0.49 microliters of the control group (Patel, 2025).

Summary of Preliminary Data: Using a capillary feeder assay, all fly groups were given a 10% ethanol and 5% sucrose solution. As Figure 4 shows, the curcumin-fed flies consumed the most of the solution, followed by the ellagic acid-treated flies and then the sucrose-fed flies (0.88 microliters vs. 0.55 vs 0.49, p-value < 0.05). After follow-up experiments on climbing activity and energy levels through wing usage were done. Data suggests that the curcumin and ellagic acid-fed flies not only ate more, but flew more and climbed more, with a 183% increase in climbing activity and a 15051.52% increase in flight activity (see Fig. 5) from the curcumin diet to the sucrose diet.

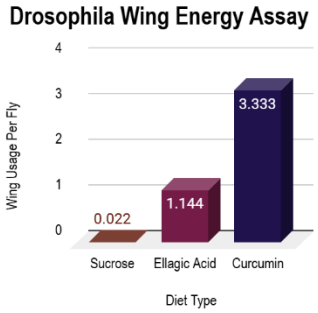

Figure 5: Energy in Drosophila Observed Through the Number of Wing Usages Per Fly in One Minute. The means usages per fly were 0.022, 1.14, and 3.33 for the sucrose, ellagic acid, and curcumin groups, respectively (Patel, 2025).

Expected Outcomes: The overall outcome of this aim is to determine how bioactive ingredients alter ethanol consumption and locomotion in Drosophila. It is expected that experimental flies will have a higher intake due to heightened CYP activity and larger energy demands. These outcomes will confirm the impact of diet on ethanol and be used for comparison against other strains of Drosophila, which mimic CYP population MAF values.

Potential Pitfalls and Alternative Strategies: We expect that the experimental dosages of the geographic ingredients may not produce clear results. Alternate strategies include increasing the dosage or exposure duration.

Specific Aim #2: Determine the impact of bioactive ingredients on CYP gene expression. The objective is to discover CYP allele transcription changes caused by diet. Our approach is to feed wild-type Drosophila on sucrose, curcumin, or ellagic acid for 6 days, then use RT-PCR to analyze gene expression in CYP6a2, CYP6a8, and CYP12d1 genes, relative to the control. Our rationale for this approach is that CYP enzymes are crucial in drug metabolism and can be altered by dietary phytochemicals, which allows us to predict future behaviors and dosages.

Justification and Feasibility: The goal of this aim is to determine if bioactive ingredients alter the expression of CYP6a2, CYP6a8, or CYP12d1 alleles in the flies. In a study by Hof-Michel in 2025, flies were given either sucrose, 0.1% curcumin, or 1% curcumin and gene expression was determined using RT-PCR after 8 days (see Figure 5). Changes were sex dependent; however, the females on the 0.1% curcumin diet experienced a large deregulation in 4 histone acetyltransferase genes, proving how curcumin, and possibly other diets can have a genetic impact (Hof-Michel et al., 2025).

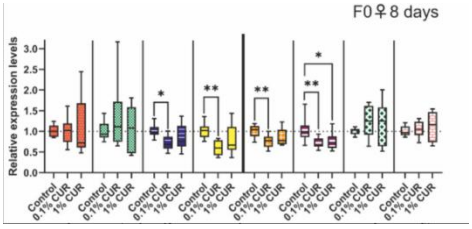

Figure 6. Gene expression in Drosophila after 8 days of being on either a sucrose, 0.1% curcumin, or 1% curcumin diet (Hof-Michel et al., 2025).

Summary of Preliminary Data: N/A

Expected Outcomes: The overall outcome is to determine diet's impact on CYP expression. We expect to see changes in CYP6a2, CYP6a8, and CYP12d1, compared to the control. This knowledge explains how changes in CYP activity will help us understand Drosophila metabolic pathways and future ways to customize treatments.

Potential Pitfalls and Alternative Strategies: We expect that diet's effect on CYP alleles may not be long-term, meaning flies must be tested at different points during exposure. Another potential pitfall could be that some alleles may be upregulated while others are downregulated, complicating the analysis of the ingredients' effect. To combat this, alleles should be analyzed independently.

Specific Aim #3: Determine if diet's effect on drug response has consistent patterns in distinct populations. The objective is to assess the effect of dietary components on populations with genetic variation. Our approach is to feed RNAi flies with downregulated CYP genes sucrose, curcumin, or ellagic acid, and quantify their locomotion compared to wild-type flies. The rationale for this approach is that populations have differing MAF values. If dietary effects are replicated in RNAi flies, we can infer that predicted drug responses in humans are location-dependent.

Justification and Feasibility: The goal of this aim is to determine if the effects of curcumin and ellagic acid are proportional in distinct populations. Previous studies show that populations have varying MAF values (Zhou & Lauschke, 2022; Figure 6). By mimicking these populations using RNAi, we can predict how people of those populations may react to drugs. Knowing that the allele frequencies in some populations differ means that drug responses should be related to the frequency of the most commonly affected CYP genes of that ingredient**.**

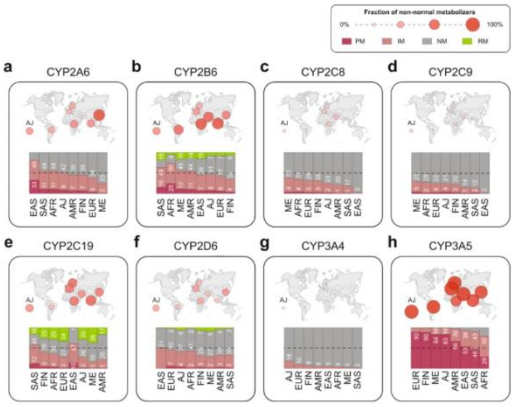

Figure 7. Frequencies of inferred population-specific metabolic phenotypes (Zhou & Lauschke, 2022).

Summary of Preliminary Data: N/A

Expected Outcomes: The overall outcome is to find how the effects of diet are reproduced in populations with genetic variation. I expect that the result will depend on which gene is silenced, which may heighten the wild-type group results. This knowledge will be used to understand how diet may have differing impacts depending on the individual who consumes it. It will also be used to understand metabolism rate and diet-gene-drug interactions.

Potential Pitfalls and Alternative Strategies: A potential obstacle is that results may not support the wild-type group results; however, it helps us understand nutrigenetics. Another pitfall is uneven food, creating disparity in gene activity changes and locomotion. This could be tracked using sulforhodamine B.

Section III: Resources/Equipment

For preliminary data, the necessary equipment is wild-type Drosophila melanogaster, sucrose, curcumin, ellagic acid, ethanol, cafe assay vials, and capillaries. Moving forward, resources such as PCR primers, RT-PCR kits, and RNAi Drosophila will be needed. All resources will be provided by Dr. C or the property of Mass Academy.

Section V: Ethical Considerations

The escape of Drosophila can create pests. To combat this, the flies will be anesthetized using CO_2 when worked with and frozen before being disposed of. All other equipment will be put in a biohazard bin.

Section VI: Timeline

The timeline is shown in Figure 7 in Appendix A.

Section VII: Appendix

Appendix A: Image of Project Timeline

STEM GANTT
Project Deadlines

To-Do

Name	Subitems	Owner	Status	Due date	Dependent On	m ID (auto generated)
Brainstorming		Saara Patel	Done	2025-12-12		10768824680
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Fill out 3 pie charts		Done	2025-10-12	10768814419	
	Fill out 3 Five-Why's		Done	2025-10-12	10768873393	
	Fill out 3 mind maps		Done	2025-10-12	10768814514	
Pick a project			Done	2025-12-13	Brainstorming	10768824667
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Fill out Pre-Project Planning docur		Done	2025-09-13	10768827605	
Do background research			Done	2025-09-30	Pick a project	10768826522
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Decide on ethnic ingredients		Done		10768829358	
	Decide on CYP genes to focus o		Done		10768836215	
	Find information on minor allele fr		Done		10768874181	
	Find model organism		Done		10768842692	
	Pre-existing knowledge		Done		10768842980	
	Knowledge gaps		Done		10768844500	
	RTPCR or ECOD?		Done		10768834542	
MSEF proposal			Done			10768842417
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Complete MSEF forms		Done		10768829853	
Finish Grant Proposal			Working on it			10768842499
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Check point 1		Done		10768819845	
	Checkpoint 2		Done		10768817606	
	Draft 1		Done	2025-12-08	10768817577	
	Draft 2		Working on it	2025-12-20	10768821503	
Preliminary Data			Done			10768875188
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Find drug dosages		Working on it		10768843387	
	Create new experimental media		Done	N/A (each 3 weeks)	10768844820	
	Transfer flies to food		Done		10768844889	
	Prepare ethanol solution		Done		10768844847	
	Perform a cafe assay		Done		10768844898	
	Analysis Data		Done		10768831497	
December fair			Done	2025-12-15		10768850221
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Create poster		Done	2025-12-08	10768839352	
	Practice poster		Done	2025-12-14	10768831978	
February Fair			Working on it			10768876049
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Repeat data for ellagic acid		Done	2/16/2025	10768839689	
	Buy RNAi drosophila		Working on it	2025-4-31	10768835967	
	Perform RT-PCF		Working on it	2025-4-31	10768848186	
	Poster		Done	2/16/2025	10768848812	
	Isolate RNA		Done	2/16/2025	11238937254	
Future work			Not done			10768858664
Subitems	**Name**	**Owner**	**Status**	**Date**	**m ID (auto generated)**	
	Create mock dosages		Not done	2025-4-31	10768858672	

Figure 7: Image of Gant Chart with Project Deadlines (Patel, 2026)

Section VIII:

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